Bone mineral density, body composition, and chronic obstructive airways disease

by

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DECLARATION

I hereby declare that this thesis is my own composition and the except where otherwise stated, the experimental work was performed by me alone.

None of the material in this thesis has been submitted for any other degree.

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Martin Li

Abstract

Inhaled corticosteroids treatments have been previously shown to decrease bone mineral density(BMD) while fluoride has been repeatedly shown to increase BMD. The effects of obstructive airway disease(OAD) and inhaled corticosteroids treatment on BMD and body composition in Hong Kong Chinese patients were studied in phase I study. For phase II of the study, the effect of fluoride on BMD and body composition in Hong Kong Chinese patients with OAD had been studied.

In phase I of this study, we had investigated the BMDs and body composition in 144 OAD patients, among them 106 (Group I consisted of 37 premenopausal female; group II, consisted of 36 postmenopausal female, and group IV comprised 33 male) were on a dosage of 800 μg inhaled corticosteroid or more a day and 38 did not take any corticosteroid(Group III consisted of 14 postmenopausal female and group V consisted of 24 male). The mean duration of taking inhaled corticosteroids was 45 ± 17 weeks (ranging from 16 to 76 weeks) for group I, 42 ± 13 weeks (ranging from 14 to 64 weeks) for Group II, and 40 ± 11 weeks (ranging from 20 to 62 weeks) for group IV. For the control group, each OAD patient was matched with two normal subjects adjusted for age(within ± 2 year), BMI(within ± 10 %) and sex. The BMDs of the total body, lumbar spine(L1-L4), femur neck, intertrochanteric region, and Ward's triangle, and the body composition of each participant was measured by dual energy X-ray absorptiometry (DEXA).

The total body BMDs of the pre-menopausal women(group I) and the OAD men not on inhaled steroids(group V) were found significantly lower than those of the controls($p<0.05$) and. The lumbar spine BMDs were found significantly lower($p<0.01$) than the controls both for OAD men(group V) and post-menopausal OAD women(group II) on inhaled steroid. Comparing with the control groups, the BMDs of the femoral neck, intertrochanteric region and Ward's triangle were significantly lower among OAD men with inhaled steroids($p<0.05$, $p<0.01$, and $p<0.05$, respectively) or without inhaled steroids($p<0.001$, $p<0.001$, and $p<0.01$, respectively).

In addition, there was significantly difference in the lumbar spine(L1-L4) BMD between the OAD patients(men and women) with and without inhaled steroids therapy.

Inhaled steroids at the dosage of 1522 ± 508 μg per day for 42 ± 13 weeks did not decrease the total body BMD. However, lower BMD was noted at the lumbar spine(L1-L4), among all the subjects using inhaled corticosteroids, and the elderly OAD male patient (group V) who had never taken any inhaled corticosteroid treatment, compared with the controls. With OAD women, their hip BMDs were less affected by inhaled corticosteroids than those men at similar age.

Pre-menopausal women treated with inhaled steroids have a higher fat mass, compared with their controls. OAD or inhaled steroid inserted insignificant effect on body composition.

In phase II of this study, the effects of fluoride and / or calcium on BMD were studied among 82 OAD patients currently on inhaled corticosteroid were studied. They were grouped by sex, age(within ± 2), and BMI(within ± 10%) and randomly allocated for Tridin (fluoride and calcium) or calcium therapy. Their response to Tridin and or calcium treatments were documented by sequential measurements of their BMDs at lumbar spine (L1-L4) and proximal hip.

Subjects developed significant side-effects with Tridin and calcium treatments 4 and 2 patients could not tolerance Tridin and calcium therapy, respectively. Other patients withdrawn from the study for the following reasons, 3 died of unrelated conditions, 1 was lost to follow up, 4 were uncooperative and 6 quitted for personal reasons(Table 7.5.a.). The remaining patients were followed for 9 months. Results were analysed accordingly, group I consisted of all the 30 pairs' patients, group II consisted of 12 pairs of male, group III consisted of 18 pairs of female, group IV consisted of 9 pairs premenopausal female and group V consisted of 9 pairs of postmenopausal female.

There was no significant difference in daily calcium intake between the Tridin group(median = 371 mg) and calcium group(median = 434 mg). The compliance was 59 ± 4(ranging from 16 to 100%) for those with Tridin and 67 ± 24(ranging from 16 to 97%) for those with calcium. Tridin group showed a lower level of hip and lumbar spine(L1-L4) BMDs than those of calcium group. However, the differences were not statistically significant. On the other hand, male subjects taken Tridin(Table 7.4.b.) showed

significantly lower Ward's triangle BMD($p<0.05$, figure 7.4 b) than those taken calcium only.

Patients responded more favourably to calcium than to Tridin therapy(table 7.7). However, this might be due to the small sample size.

The BMDs of the group given Tridin were lower than those of the group given calcium. Tridin or calcium treatment did not increase BMDs at the lumbar spine(L1-L4) or the hip. Site specific bone lose due to Tridin treatment was observed in male and premenopausal female OAD patients, whose bone density lost more rapidly at hip than lumbar spine. On the contrary, no site specific lose was observed among the calcium treatment group. Further studies are needed to determine the effective dose of Tridin or calcium for the OAD patients.

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CONTENTS

LIST OF ABBREVIATIONS

B	Partial regression coefficients
BMC	Bone mineral contents (g / cm) in ROI from DEXA measurements
BMD	Areal bone mineral density (g / cm^2) as measured with DEXA
BMI	Body mass index = body weight (kg) / body $height^2$ (M)
BSU	Bone structure unit
COAD	Chronic obstructive airway disease
Ca	Calcium ion
Caflu®	Monofluorophosphate containing preparations
CV	Coefficient of variation
DEXA	Dual energy X-ray absorptiometry
F	Fluoride
PFR	Peak flow rate
FEV1	Forced expiatory volume in one second
g	gram
L1	First lumbar vertebra; others are denoted by numbers 2-4
L1-L4	First to fourth lumbar vertebra
LBM	Lean body mass
LMI	Lean mass index = Lean body mass(kg) / body $height^2$ (M)
M	meter
MFP	monofluorophosphate
mg	milligram
n	number of items / entries
NaF	Sodium fluoride
kg	kilogram
OAD	Obstructive airway disease
PTH	Parathyroid hormone
Tridin®	Monofluorophosphate containing preparation

QDR-1000	DEXA instrument from Hologic, Inc., Waltham, Massachusetts
QDR-2000	DEXA instrument from Hologic, Inc., Waltham, Massachusetts
R^2	Variance
r	Correlation coefficient
ROI	Region of interest
SE B	Standard error
SD	Standard derivation
TBBM	Total body bone mass (BMC)
TBBMD	Total body bone mineral areal density (BMD)
VC	Vital capacity

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Chapter 1 Obstructive airway disease: Public health and clinical aspects

1.1. Background

Oral steroid therapy is well known for its adverse side effect on bone density. The trend is be replace oral steroids by inhaled corticosteroids therapy for the treatment of obstructive airway diseases(OAD) such as asthma and chronic obstructive airway disease(COAD)(Report, I. C., 1992).This has led to investigations into whether inhaled steroid therapy leads to bone loss.

The measurement of bone mineral density with dual energy X-ray is now a valuable tool for studies of body composition and skeletal status for the health and the disease. Rapid, accurate and precise measurement can be repeated with much lower doses of radiation. It also allowed total body as well as regional skeletal bone mineral density to be measured.

The relationship between inhaled steroid therapy and osteoporosis will be studied in Chinese asthmatic patients. The mean daily calcium intake of Hong Kong Chinese is less than 500 mg per day(Lau, E. , Woo, J. et al, 1992), and inhaled steroids may have a larger impact on bone mineral density(BMD) than in Caucasians. In phase I of this study, the effects of inhaled steroid on BMD and body composition will be investigated. Premenopausal and postmenopausal asthmatic Chinese women and asthmatic Chinese men age 45 or above will be studied. The effect of

obstructive airways disease *per se* on body composition and BMD will also be investigated.

In phase II of this study, the effect of fluoride (Pouilles, J. M., Tremollieres, F. et al, 1991; Riggs, B. L., WM, O. F. et al, 1994) in preventing bone loss in men and women with inhaled steroid therapy for asthma and chronic obstructive airway disease (COAD) will be investigated.

1.2. Magnitude of the problem

1.2.1. Asthma

In England, diagnosis of asthma is coded according to the rules of the International Classification of Disease (ICD). These rules are revised periodically, and changes in coding rules have produced small artificial increases in death-rates in 1979 and in 1984. Currently, 10% of children and 7.5% of adult(totally 2.5 million people) in England and Wales are having asthma.

Prevalence rates vary markedly between different countries, accounted for in part by differing diagnostic approaches and a more important source of error is that due to diagnostic uncertainty. Under the age of five, deaths attributed to asthma are exceeded by deaths ascribed to other respiratory disease (pneumonia, bronchitis and bronchitis, and upper respiratory tract infection). Asthma death-rates in older children and young adults are probably more reliable in that other respiratory disease are often less fatal. The actual numbers of childhood death in England are few; less than 10 deaths per year among 5 and 14 year age group.

In the Western countries, the prevalence varies between 12% and 23%, whereas in Asia the prevalence is among 2% and 9%(Leung, R., Bishop, J. et al, 1994). There is also accumulating evidence that the prevalence of asthma is increasing in both the Western and Asian countries(Lau, Y. L., Karlberg, J. et al, 1995).

The prevalence of asthma in children aged 3 to 10 in Hong Kong is 6%(Lau, E., Egger, P. et al, 1995), similar to that in Singapore(4.8%) and in Taiwan(5.8%) but is lower than that in Japan(11%) and in Malaysia(13.8%)(Leung, R. and Ho, P., 1994). Recently, study has shown the age-specific prevalences of asthma among Hong Kong young children were 10% at age 7, 8% at age 12, and 7% at age 15 (Leung, R.,Bishop, J. and Robertson, C. F., 1994).

The number of death due to asthma in Hong Kong was 3.2 per million in 1976 and rose to 6.7 per million in 1985(So, S. Y., Ng, M. M. et al, 1990). Similar trend has been observed elsewhere.

1.2.2. Chronic obstructive pulmonary disease

Chronic obstruction airway disease (COAD), is a destructive and obstructive disease of the airways associated with disruption of the ciliated mucosa and airway obstruction. Damage to alveolar walls and permanent loss of the pulmonary capillary bed occur. COAD occurs commonly among the elderly in Hong Kong, especially among the smokers.

Symptoms of OAD patients vary from occasional wheeze to serve respiratory difficulty leading to hospitalisation. OAD patients account for 8%

of total hospital admission in a Hong Kong hospital(Wong, T. W. and Lam, K. W., 1994). Most of the patients required life-long treatment.

Between 1989 to 1994, OAD patients account for 3.3 to 3.7% of the total hospital admission(table 1.1), and OAD mortality account for 6.9 to 8.2% of the total deaths in Hong Kong. The OAD mortality ratio between male and female was about two. OAD patients in Hong Kong had a mortality rate of twice as much as those with other diseases.

Between 1984 to 1994, OAD was one of the ten major causes of death in Hong Kong(Department report, 1984-1985; 1993-1994).

1.2.3. Prevalence of osteoporosis in Hong Kong

The incidence rate of hip fracture in Hong Kong has increased 3-fold since 1966 to reach 9 per 1000 in men and 13 per 1000 in women aged 80 and over in 1989(Lau, E. M. and Cooper, C., 1993). Similar observations have been made in Singapore(Lee, S. and Lee, K., 1988) and Japan(Orimo, H., 1990). Another Hong Kong study has indicated that about 200,000 patients among a population of 6 million were affected by osteoporosis(Pun, K. K., Wong, F. H. et al, 1991).

Osteoporosis is a major public health problem in most developed countries. In the United States, it has been estimated that 20-25 million people are osteoporotic which manifested as 240,000 hip fractures, over 500,000 vertebral fractures, and 170,000 forearm fractures annually(Peck, W., 1995).

1.2.4. History of asthma care

Asthma is recognised nearly 4000 years ago in China and was treated with leaves of the plant *Ephedra*(Teeling-Smith, G., 1990). It is not until 1920s that ephedrine is first used in Western medicine. The word asthma derives from a Greek word meaning difficulty in breathing. Hippocrates has described asthma and recognised that it could be fatal. By the 16th century, it is noted that asthmatics were affected by feather pillows, dust and changes in weather(Teeling-Smith, G., 1990).

1.2.5. Treatment of OAD

Theophyllines, bronchodilaters, and corticosteroids have been used to treat OAD. Theophyllines are bronchodilators with a central stimulant action. Side-effects range from nausea, vomiting, and sudden deaths have been reported. Other bronchodilaters included short acting beta-2 agonists which stimulate the beta-2 adrenergic receptors in the bronchial smooth muscle, causing relaxation. They also enhance mucocillary clearance and decrease vascular permeability. Inhaled long acting beta-2 agonists are usually given for their protective effect against bronchospasm. They are relatively free of side-effects and are of low toxicity, as compared with long-acting oral beta-agonists and theophyllines. However, tremor, palpitation, and headache may occur in some patients. Anticholinergics block post-ganglionic vagal pathways, so reducing vagally-induced bronchconstriction. Side-effects include blurred vision, urinary problems, and dry month.

Prevention and anti-inflammation are the two major roles of corticosteroids in the treatment of OAD. They act through a variety of cellular

and, local hormonal and chemical pathways, and reduce mucus viscosity and increase beta-receptor responsiveness.

Inhaled corticosteroids in low doses are used for the management of mild to moderate asthma, and higher doses (more than 800 μg a day) are used in patients with more serve asthma. They control the underlying inflammation and thereby reduce the severity and frequency of acute attacks. The dose may be temporarily increased to give added protection at times of increased risk, such as during an upper respiratory tract infection. It is believed that inhaled corticosteroids may prevent the long-term damage to the lungs that might have otherwise occur in OAD patients. For most cases, inhaled steroid is the drug of choice for good control(Barnes, N. C., 1993; Lai, C. K., Chan, C. H. et al, 1995).

1.3. Side effects of Glucocorticoid in OAD patients

Systemic steroids are well known for their adverse effects on bone. They can lead to progressive loss of trabecular bone, hence increasing the risk of fractures The effects are likely to be dose and duration related. Other side-effects include adrenal suppression, raised blood glucose, psychiatric problems, weight gain, thin skin, redistribution of fat, oral thrush, and hirsutism in woman.

It has been previously reported that Glucocorticoid treatment are associated with increased bone resorption. BMD may be reduced by 10-20 % at the hip and the spine(Brandli, D. W., Golde, G. et al, 1991). Decrease

in calcium absorption from the intestinal tract, inhibition of osteoblast and increase in urinary calcium loss may occur. However, administration of glucocorticoids on alternative days does not reduce the risk of bone loss(Medici, T. C. Rüegsegger, P., 1990).

One study has shown that glucocorticoids suppressed growth in children as a result of reducing circulating oestrogen or testosterone, through actions on the pituitary, gonad or adrenal glands(MacKenzie, C. A., Weinberg, E. G. et al, 1993). In other studies no evidence of adrenal suppression occurred in children, if four or fewer courses a year were given, with each course less than three weeks(Balfour-Lynn, L., 1986).

1.4. Side effects of inhaled corticosteroids in OAD patients

In recent years inhaled corticosteroids have been prescribed in higher dose than previously. This has caused increasing concern about the systemic side-effects similar to those associated with the oral use, particularly when the inhaled doses have exceeded 1000 μg a day.

The effects of systemic corticosteroids administration on children's growth have been extensively studied (Balfour-Lynn, L., 1986; Shohat, M., Shohat, T. et al, 1987). There was no suppression of normal growth in children who received less than 800 mg a day of beclomethasone or budesonide, for up to eight years. In pre-school children, no growth suppression was found at doses less than 400 μg a day. On the other hand

similar dose of inhaled beclomethasone dipropionate (Wolthers, O. and Pedersen, S., 1991) has been shown to be effectively in leg growth suppression in another study. Recently, several studies reported that bone density was not affected in asthmatic children and women taking inhaled beclomethasone for 6 to 12 months(Baraldi, E., Bollini, M. C. et al, 1994; Herrala, J., Puolijoki, H. et al, 1994). However, one Hong Kong study reported a decrease in BMDs of lumbar spine, neck of femur, and trochanter in female asthmatic patients, after taking budesonide or beclomethasone dipropionate for an average of 40 months(3-180 months). In contrast, there was no statistically significantly differences in BMDs between those male patients and their matched control subjects(Ip, M., Lam, K. et al, 1994).

At higher dose, inhaled steroids inhibits adrenal production of androstenedione secretion, which is of particular concern among postmenopausal woman, since the conversion of androstenedione to oestrogen in adipose tissue is their principle source of oestrogen(Crilly, R. G., Cawood, M. et al, 1988).

1.5. Trend of asthma therapy in Hong Kong

Inhaled steroids become the primarily choice for asthma therapy in Hong Kong. During 1984-1986, oral anti-asthmatic agents (beta-agonists) were used more commonly than inhaled drugs, and inhaled therapy mainly consisted of non-selective beta-agonists. Steroids were rarely used(Kumana, C. R., So, S. Y. et al, 1989). In 1987, aminophylline was mostly used to treat

chronic adult asthma, and inhaled beta-agonist was used in the maintenance therapy for adult and children asthmatics. Inhaled steroid was only the second line drug. In 1992, inhaled steroids become the drug of choice in treating asthmatic patients in Hong Kong(Ip, M. S., So, S. Y. et al, 1993).

Table 1.1 Details of OAD admission in Hong Kong between 1989-1994

	International Classification of Disease detailed list no. 1975 revision 9													
	ICD:490, 491 [a]		ICD:492,493 [b]		ICD:494 [c]		ICD:495, 496 [d]		ICD:490-496 [e]		ICD:001-999 [f]		Percent of admitted	Percent of deaths
Year	Admitted	Deaths	Admitted	Deaths	Admitted	Deaths	Admitted	Deaths	Admitted	Deaths	Admitted	Deaths	OAD cases	due to OAD
89-90	2387	71	9058	426	913	59	18141	1567	30499	2123	826735	28485	3.7	7.5
90-91	2050	50	8264	505	927	54	18309	1535	29550	2144	820655	29201	3.6	7.3
91-92	2009	80	8119	351	893	65	16830	1472	27851	1968	833450	28682	3.3	6.9
92-93	2811	319	9202	171	1222	60	19769	1944	33004	2494	898180	30526	3.7	8.2
93-94	3218	270	9960	166	1089	67	20332	1716	34599	2219	950362	30222	3.6	7.3

a	490,491	Bronchitis, chronic and unspecified
b	492,493	Emphysema and asthma
c	494	Bronchiectasis
d	495,496	Other chronic obstructive pulmonary disease
e	490-496	All type of OAD diseases
f	001-999	All type of diseases listed in the International Classification of Disease(ICD)

Data were extracted from Director of Medical and health services: departmental reports 1989-1994.

Chapter 2: Osteoporosis: Public health and clinical aspects

2.1. Bone Biology

Bones are composited of calcium and phosphorous crystals, held together by protein fibres. Calcium produces the strength and rigidity in bones, and proteins allow flexibility. Other minerals that help holding bone cells together are fluoride, sodium, potassium and magnesium.

Bone resorption by the osteoclast plays an essential role in the homeostasis of both the skeleton and serum calcium. This cellular process is essential in the growth and remodelling of bones, and it is tightly coupled to the process of bone formation by the osteoblast. Coupling of these two cell types are necessary for the maintenance of skeletal health. The disruption of the coupling between bone resorption and formation may lead to conditions such as osteopetrosis, osteosclerosis or osteoporosis.

2.2. Skeletal Organisation

The skeleton consists of mostly enchondral bones, which are the results of secondary transformation of cartilage, and membranous bone such as the flat bones of the skull, which are originated from the mesenchyme. The enchondral bone has two components, peripheral (the compact bone or the cortical bone) and central (bone marrow). The cortical bone accounts for 80% of the total skeletal mass and is composed of plates bone called

lamellae. Lamellae are organised about the central Haversian nutrient canals. The bone marrow consists of a honeycomb of vertical and horizontal bars called the trabecular or woven bone, and it is filled with red marrow and fat. In adult human, trabecular bone is the sole repository of red marrow, localised in most parts of the vertebral bodies, the long bones and pelvis. The metaphyseal ends of adult long bones also contain trabecular bones but not bone marrow.

2.3. Bone remodelling

Bone remodelling is a coupled process, the resorption phase of bone remodelling in cortical bone takes about 15 days. It begins with the formation of bone multicellular unit(BMU) that consists of tunnel (cutting cone) drilled out by advancing osteoclasts. Bone formation in the BMU begins with the differentiation of preosteoblasts into osteoblasts. Afterward, they form the matrix, which becomes mineralised and fills out the tunnel except for the central Haversian system constitutes a new cortical bone structure unit (BSU).

Bone remodelling in cancellous bone is identical, except that the resorption period lasts about 50 days and can be subdivided into three stages: the osteoclastic stage, the mononuclear stage and the preosteoblastic stage. Matrix formation lasts for 15 days followed by mineralization for another 130 day. Thus, it takes around 150 days to form a new cancellous BSU.

2.4. Effect of corticosteroids on bone remodelling

The major effect of corticosteroids appears to be the depression of osteoblastic function. This can be demonstrated histomorphometrically as a reduction in mean wall thickness, lamella thickness, osteoid surface and osteoid seam width(Aaron, J. E., Francis, R. M. et al, 1989). In tissue culture experiments, both osteoblastic replication and differentiation are inhibited by corticosteroids(Lukert, B. P. and Raisz, L. G., 1990). The osteoblasts also had a shortened life span(Dempster, D. W., Arlot, M. A. et al, 1983). In contrast to osteoblastic activity, osteoclasts were not abundant at resorption surfaces. Thus, the net loss in bone mass during corticosteroids treatment could be the result of reduced bone formation rather than increased osteoclastic activity(Lundy, M. W., Stauffer, M. et al, 1995).

Elevated parathyroid hormone (PTH) level during corticosteroids therapy causes reduction of calcium absorption from bowel and its the renal reabsorption. It also increases the formation of new remodelling units, and the net decrease in bone mass would be amplified.

2.5. Corticosteroids induces osteoporosis

The microanatomical appearance of corticosteroid-induced osteoporosis differs from that of idiopathic osteoporosis(Aaron, J. E., Francis, R. M., et al 1989). The numbers of trabecular bone and their surface area are relatively preserved in corticosteroid induced osteoporosis, but individual lamella plates are very thin. For idiopathic osteoporosis, the

major driving force to bone loss is osteoclastic resorption. The trabecular width is relatively preserved, but the lamellae were perforated by resorption, with a loss of trabecular surface and continuity.

2.6. Factors affecting BMD

2.6.1. Peak bone mass

Development of osteoporosis appears to be related to the peak bone mass attained at young adulthood and to the rate of bone lose thereafter. Peak bone mass is attained between the ages of 20-35(Bonjour, J. P., Theintz, G. et al, 1991; Sugimoto, T., Tsutsumi, M. et al, 1992). This age varies with sex, race, calcium intake, geography location and exercise.(Ho, S. C., and Hsu, S. Y. et al, 1993; Ho, S. C., and Leung, P. C. et al 1994).

2.6.2. Ethnic factors

Several studies suggested BMD varies in subjects of different ethnic origins. Chinese, Korean and Japanese of the same age have similar BMD, and the optimal peak bone mass achieves at the age between 30-39(Norimatsu, H., Mori, S. et al, 1989; Bonjour, J. P.,Theintz, et al, 1991; Sugimoto, T.,Tsutsumi, M., et al, 1992). In contrast, Caucasians reach their peak bone mass at around 30. The mean BMD of Korean woman was 11.1 % lower than their Caucasian counterpart. Other study revealed that American Blacks have higher BMD than American Caucasians(Côté, K. D. and Adams, W. C., 1993; Bell, N. H., Gordon, L. et al, 1995).

One study on Japan-born and US-born Japanese American women reported that the BMD among US-born Japanese American was higher than those born in Japan(Kin, K., Lee, J. H. et al, 1993). This suggests a modification effect of the environment on genetic factors.

2.6.3. Aging

Bone loses with aging(Lips, P., Courpron, P. et al, 1978; Kragstrup, J., Melsen, F. et al, 1983). Like most biological process, bone remodelling is not entirely efficient, the amount of new bone formed is not always equal to the amount previously removed, so that a small bone deficit persists after each cycle. This inefficiency is called remodelling imbalance and the accumulation of this deficit over the years may lead to osteoporosis.

The pattern of age related bone loss varies with different types of bone. In cortical bone, there is a prolonged slow phase of bone loss that begins at about age 40 in both males and females. The initial rate of loss of 0.3 to 0.5 % per year increases with age, but declines or stops very late in life span(Mazess, R. B., 1982). In women, there is a more rapid phase of bone loss that begins at menopause and may reach 2-3 % a year for 8-10 years after their menopause. Both men and women begin to lose trabecular bone at the age of 30-35(Mazess, R. B., 1982).

2.6.4. Calcium intake

Greater calcium intake early in life may have a beneficial effect upon adult bone mass, whereas increase dietary intake at later life seems to have

lesser effect on bone mass. The daily calcium intake in Hong Kong Chinese is about 350-450 mg per day(Lau, E. M.,Woo, J., et al, 1992), but in Finland it is about 1g in adult(Kroger, H. and Laitinen, K., 1992); 1.6g in boys and 1 g in girls(Andersen, L. F., Nes, M. et al, 1995; Andersen, L. F., Nes, M. et al, 1995).

2.6.5. Oestrogen

Oestrogen deficiency is the major cause of decreased skeletal mass in woman. Postmenopausal bone loss is associated with falling oestrogen level, and some success in skeletal preservation has been achieved by using hormone replacement therapy after menopause or ovariectomy. Skeletal growth and maturation in girl at puberty is associated with a rise in oestrogen level. Bone mineral density is lower in a hypogonadal woman regardless of its cause(Richelson, L., Wahner, H. et al, 1984). Moreover, a postmenopausal woman will lose 13% of her total bone mass within 15 years after her menopause.

It has been demonstrated that oestrogen inhibits the Interleukin-6(IL-6) production by cultured bone marrow stromal and osteoblastic cell lines, as well as primary bone cell cultures from rats and human(Girasole, G., Jilka, R. et al, 1992). (With oestrogen loss, this inhibitory effect is lessened, resulting in an up-regulation of IL-6 which stimulates osteoclasts production and then increases bone resorption). Injection of anti-IL-6 antibody has been shown to inhibit osteoclast activity in human(Klein, B., Wijdenes, J. et al, 1991).

2.6.6. Alcohol consumption

Alcohol consumption has been implicated as an important aetiological factor in the development of osteoporosis in men(Cohn, K., Sartoris, D. et al, 1992). The incidences of rib and vertebral fractures were higher in alcoholics(Schapira, D., 1990). In one study (Odiva, C. V., Safi, I. et al, 1995), the effect of prolonged alcohol consumption on bone mineral density in both black(n=21) and white(n=19) male subjects without significant hepatic disease were evaluated. No significantly differences were found in BMD values for lumbar spine, total hip, and femoral neck were found between the alcoholics and their control subjects. However, in white subjects, age($p = 0.013$), and duration of alcohol intake ($p = 0.002$) had significant independent effects on the BMD of spine. However, the duration of alcohol intake ($p = 0.029$) was the only factor with independent effect on the bone density of hip. In black subjects, age was the only independent factor affecting the bone densities of spine and hip($p = 0.009$ and 0.014, respectively).

2.6.7. Cigarette smoking

Smoking has been shown to be associated with low bone mass in young pre-menopausal female(Mazess, R. B. and Barden, H. S., 1991), and elderly men(Pocock, N. A., Eisman, J. A. et al, 1989).

2.7. Physical activity and BMD

BMDs are higher in physically active individuals. One recent cross-sectional study on pre-menopausal women has shown that the BMDs at the lumbar spine and hip of the walkers and aerobic dancers were higher than those of the non-exercisers(Alekel, L., Clasey, J. L. et al, 1995). These findings suggested walking and aerobic dancing exercise may provide the physically active pre-menopausal women with higher lumbar and femoral BMDs than that of the sedentary females.

The site specific changes in BMD of hip are observed(Lee, E. J., Long, K. A. et al, 1995). Basketball player has shown the highest hip BMD. This is followed by swimmer, moderately active control subjects and sedentary control subjects.

2.8. Body composition in Chinese subjects

Body composition analysis, particularly the estimation of fat-free mass and total body fat, forms part of the nutritional assessment process. It offers more information than body mass index(BMI), since changes in body weight may be the result of changes in either component. Previous report has revealed that the BMD of female is associated with body fat mass(Beshyah, S. A., Freemantle, C. et al, 1995). Thus, it is important to study the body composition of human beings. Body fat mass is related to blood pressure and other cardiovascular disease risk factors, glucose intolerance, insulin resistance, BMD, and osteoporosis.

In the past decade, non-invasive dual energy X-ray absorptiometry(DEXA) had been developed for the estimation of body composition(Fuller, N. J., Jebb, S. A. et al, 1992; Johansson, A. G., Forslund, A. et al, 1993). It was found to be a more precise method of measuring body composition compared with skin-fold thickness measurement.

Previous studies among Hong Kong Chinese have shown that both lean body mass and body fat in addition to body weight are significant associated with BMD in woman aged 31 to 40(Pun, K. K., Wong, F. H., et al 1991). Moreover a comparative study on BMD between 575 healthy premenopausal and postmenopausal Chinese women living in Hong Kong and Taiwan have concluded body weight is a significant predictor of BMDs for hip and spine(Lau, E. M. C., Tsai, K. S. et al, 1995).

Chapter 3 Phase I: Body composition and bone mineral density in obstructive airway disease patient and normal control subjects: Objectives, Subjects and methods

3.1. Objectives

The objectives of this phase of the study were to compare the body composition and the bone mineral density (BMD) of obstructive airway disease (OAD) patients with normal control subjects, and to study the effects of inhaled steroid treatment on the body composition and BMD of the OAD patients. The research questions are:-

3.1.1 Are the fat mass, lean mass and percentage fat mass of OAD patients lower than that of normal control subjects?

3.1.2 Are the bone mineral densities at the hip and spine lower in OAD patients?

3.1.3 Are the fat mass, lean mass and percentage fat mass of OAD patients taking inhaled steroids than that of OAD patients not taking inhaled steroids?

3.1.4 Are the bone mineral densities at the hip and spine lower in OAD patients taken inhaled steroids?

3.2. Subjects and methods

3.2.1 OAD patients

3.2.1.1 Disease definition and selection criteria

Patients who fulfilled the following criteria were recruited:-

a) Diagnosed to have chronic obstructive airway diseases(COAD) or asthma by a qualified physician with membership of Royal College of Practitioner, bearing the ICD coding:490-496.

b) Aged 18 and over.

c) Have never had a history of metabolic bone disease.

d) Have been using inhaled steroid regularly for at least 3 months

e) Have never had a history of chronic systemic steroid use for more than 1 month continuously, more than 4 booster courses or having systemic steroids in the previous 3 months(Ip, M.,Lam, K., et al, 1994).

Patients were recruited from the Specialist Respiratory Disease Clinic at the Prince of Wales Hospital and the Family Medicine Clinic at the Lek Yuen Health Centre in Shatin. All eligible patients who were registered with these clinics were recruited into our study. The study was conducted from January 1995 to December 1995.

3.2.1.2. Normal Control subjects

The normal control subjects were volunteers among medical and non-medical staff and medical students from the Prince of Wales Hospital, Shatin. A notice introducing the surrey was sent to the staff members and subjects were recruited consecutively.

Control subjects were matched individually with the patients for sex, age(within ± 2 year), and body mass index (within ± 10%).

3.3. Power of estimation

In order to detect a statistical difference of 0.5 with a statistical power of 0.75 and type 1 error of 5% between the OAD patients and the control groups. The minimum number of patients required for each group is 35. If the statistical power is 0.8, the minimum number of patients required for each group is 39.

3.4. Survey methods

OAD patients were interviewed using a standardised structured, questionnaire as they attended the clinics(Appendix 1). They were then requested to have their body composition and bone mineral density measured.

Informed consent was obtained from all subjects before the interview and laboratory measurements.

3.5. Questionnaire

A standardised structured questionnaire was developed to measure the dietary calcium intake, physical activity, medical history, reproductive history(for woman), and history of drug treatment and other medical conditions of the subjects. The questionnaire was compiled partly from a validated questionnaire used previously in studying osteoporosis among Hong Kong Chinese(Lau, E. . and Donnan, S., 1988) (Appendix I).

Dietary calcium intake was assessed by recording the frequencies of consumption of 17 Chinese food items during the previous week. These items have previously been found to be the main source of calcium intake in the Chinese diet. The dietary calcium intake of each food item was calculated as the product of the intake frequencies during the past week, the weight of an average proton size, and the calcium content of the standard portion size which was published in the South East Asia Food composition table. Thus, the total calcium intake would be the sum of these products.

Physical activity was measured by the frequencies of several of load-bearing activities which had been performed during the past week.

3.6. Body composition and bone mineral density measurement

Body composition and bone mineral densities of total body, lumbar spine(L1-L4), and left proximal hip were measured with dual x-ray densitometry using Hologic QDR-2000 machine(Hologic, MA, USA). This machine emits a very low dose of X-ray and the effective dose is less than

27mR (0.27mSV), which is approximately half of the dosage emitted for a standard chest X-ray. Thus, additional protective procedure was needed to shield the patient, operator or room from the exposure.

3.6.1. Body composition analysis

Lean mass, fat mass, and body fat percentage were analysed with Hologic enhanced array total body software version 5.67A according to the protocol supplied by the manufacturer.

3.6.2. Lumbar spine and proximal hip bone mineral density analysis

BMD at the lumbar spine(L1-L4) was analysed with Hologic array spine medium software version V4.74A:1. The BMD at the left proximal hip was analysed with Hologic array left hip medium software version V4.59.A:1 according to the protocol supplied by the manufacturer. BMDs of the Ward's Triangle, intertrochanteric region and femoral neck were also measured.

3.6.3. Routine quality control of measurements

Standardisation procedure was performed daily by scanning an Hologic arthropromatic phantom according to the protocol supplied by the manufacturer. The results of these calibrations were entered into the quality control database provided. The C.V. was measured, and it was 0.42 % for BMD. No drift was seen during the overall period of investigation.

3.6.4. Precision on patient repositioning

To study the CV of repositioning, 20 normal subjects were scanned once and then again after repositioning. The CVs obtained were 0.7 % for spine, 1.2 % for femoral neck, 1.4 % for intertrochanteric region, and 2.8 % for Ward's triangle. Our data were similar to those previously reported(Kelly, T. L., Slovik, D. M. et al, 1988; Devogelaer, J. P., Baudoux, C. et al, 1992; Slosman, D. O., Rizzoli, R. et al, 1992).

3.7. Statistical methods

Differences in life-style factors between OAD patients and control subjects were compared by paired t-test or chi-squares test.

Multiple regression was used to compare the BMDs and body composition of the patients with the control subjects, while adjusting for the life-style factors.

The body composition and bone mineral density measurements between the OAD patients and the control subjects, and between the OAD patients who were with or without steroid therapy were compared by paired t-test.

3.8. Bone mineral density of normal control subjects

The BMDs of the normal control subjects were shown in(Appendix 3). Four hundred and twenty-five normal Hong Kong Chinese females and 163

normal Hong Kong Chinese males were recruited according to Hologic normal control standard protocol.

Chapter 4 Phase II: Fluoride in the treatment of osteoporosis

4.1. Introduction

The ideal treatment for osteoporosis is to increase bone density sufficiently to reduce the risk of fracture. Many of the currently used therapies act mainly by reducing the rate of bone loss, such as calcium, oestrogen, calcitonin and bisphosphonate. Fluoride is one of the many agents known to increase vertebral bone density. Its action on bone was noted from the observation that the trabecular bone density of the axial skeleton increased in fluoride poisoning cases. Moreover, a lower incidence of osteoporosis was observed in areas with high levels of fluoride in the drinking water(1-1.2 mg / liter) (Bernstein, D. S., Sadowsky, N. et al, 1966; Kroger, H., Alhava, E. et al, 1994; Cauley, J. A., Murphy, P. A. et al, 1995). Sodium fluoride is first used to treat vertebral osteoporosis(Rich, C. and Ensinck, J., 1961). Recently, several studies of sodium fluoride and di-sodium monofluorophosphate combined with calcium supplements or vitamin D had been carried out(Reginster, J. Y., 1995). All showed that fluoride is an effective agent in increasing trabecular bone mass, but questions remain regarding the quality of the new bone and the efficacy of fluoride in decreasing the rate of vertebral fracture. In addition, its side effects are common. Moreover, cortical bones in fluoride treated patients were reported to be more fragile(Gutteridge, D. H., Price, R. I. et al, 1984). A four year placebo-controlled study on sodium fluoride carried out in U.S. shown that

there was an increase in BMD but fracture rates remain constant(Riggs, B. L., Hodgson, S. F. et al, 1990).

A survey on the effect of fluoridated drinking water was conducted in Finland with 3222 postmenopausal women aged 47-59 years. A total of 969 women who had used fluoridated drinking water (1.0-1.2 mg/l) for over 10 years were compared with 2253 women with low levels of fluoride in drinking water (<0.3 mg/l). BMD of the lumbar spine was slight higher in the fluoride group, but the BMD of the femoral neck was similar between the two groups. There were no significant differences between the groups in the prevalences of self-reported fractures(Kroger, H., Alhava, E. et al 1994).

4.2. Mechanisms of action

4.2.1. Antiresorptive effect of fluoride

Fluoride ions replace hydroxyl ions in the calcium hydroxyapatite crystals of bone to form fluoroapatites, which increase the crystallinity and reducing the solubility of bone minerals, making them more resistant to the resorptive processes(Moreno, E. C., Kresak, M. et al, 1977).

4.2.2. Force-oriented osteogenic effect of fluoride

Fluoroapatite produces stronger piezoelectric currents than that of the normal hydroxyapatite, thus stimulates more intensely the activation and

osteogenic activity of the osteoblasts along the line of mechanical forces(Bassett, C. A., 1968).

4.2.3. Biochemical osteogenic effect

Fluoride inhibits the osteoblast-specific acid phospho-tyr protein phosphatases and results in the building up of the phospho-tyr-proteins in the osteoblasts and enhances the mitogenic and bone forming activities of these cells(Lau, K. H., 1987).

4.3. Effect of fluoride salts on BMD: results of clinical trials

Oral ingestion of 50 to 80 mg sodium fluoride a day(22.6 mg to 36.2 mg fluoride ion) increases bone mass by about 10 % a year in 80% of treated patients(Kelly, T. L., Slovik, D. M., et al, 1988; Riggs, B. L., Hodgson, S. F., et al, 1990; Devogelaer, J. P., Baudoux, C., et al, 1992; Rizzoli, R., Chevalley, T. et al, 1995)(Table 4.1). There have been many studies showing conflicting results in vertebral fracture frequencies with different fluoride preparations. In a prospective two-year study, patients treated with fluoride(50 mg NaF a day) showed a significantly lower rate of new vertebral fractures compared with patients having a variety of other commonly used treatments(Mamelle, N., Meunier, P. J. et al, 1988). A four-year study revealed that vertebral fracture rate was not affected by fluoride intake(75 mg a day supplemented with 1500 mg calcium), but nonvertebral fracture rate was significantly increased by three folds in the treatment group(Riggs, B. L., Hodgson, S. F., et al, 1990). Moreover, BMD increased by 35 %, 12 %

and 10 % at the lumbar spine, femoral neck and trochanteric area respectively over the study period, but the BMD decreased by 4% at the shaft of the radius. Fifty women from this sodium fluoride group were followed for further two years with a reduced dose of fluoride. In these women, vertebral fracture rate was reduced and BMD was increased by 8.7 % over the six-year period(Riggs, B. L., WM, O. F., et al, 1994). It appears that high vertebral fracture rate was associated with high fluoride doses and low fluoride doses resulted in lower vertebral fracture rate.

4.4. Effect of fluoride on bone histomorphology

Histomorphology studies showed bone fluoride content increased with the length of fluoride ingestion. Trabecular osteoid surfaces were increased by 96% without significant increase in trabecular resorption surfaces in one French study on postmenopausal female and male with at least one non-traumatic vertebral crush fracture(Meunier, P. J., 1990). One study showed 5.4 % increase in bone apposition rate at lumbar spine(L2-L4), and 23.5 % decrease in trabecular space in postmenopausal women and men with known mild osteoporosis treated with 50 mg slow-release sodium fluoride and 50 μg 25-hydroxyvitamin D_3 supplement a day for two years(Zerwekh, J. E., Hagler, H. K. et al, 1994). In contrast, bone biopsies obtained from a 4-year study with 75 mg NaF and 1500 Ca mg/day showed no significant difference in mineral apposition rate between fluoride treated group and placebo treated group. The bone fluoride content rose throughout the treatment period. Anyhow, evidences for fluoride induced osteomalacia were

observed from prolonged mineralization lag time, increased osteoid thickness, and defects in mineralization(Lundy, M. W., Stauffer, M., et al, 1995).

4.5. Compliance with sodium fluoride therapy

NaF could be effective in the treatment of bone loss, but it is incompatible with calcium supplements or with calcium rich meals, because they combine and form CaF_2, which is practically insoluble and impedes the absorption of fluoride in the gastrointestinal tract. Patient compliance is reduced by the formation of the gastrointestinal irritant hydrofluoric acid, the development of peripheral pain syndrome, the incidence of occasional vomiting(in 30 % of patients) and stress fracture(Mamelle, N., Meunier, P. J., et al, 1988). Recently, several studies have reduced some of the above complications by using a time released monofluorophosphate (MFP) preparation(Delmas, P. D., Dupuis, J. et al, 1990; Rizzoli, R., Chevalley, T., et al, 1995; Sebert, J. L., Richard, P. et al, 1995) or slow-release preparation of fluoride(Zerwekh, J. E., Hagler, H. K., et al, 1994).

4.6. Contradiction of fluoride treatment

The major side-effect of fluoride therapy is the possible increase in the fractures of the peripheral skeleton. Occurrence of such fractures may be reduced with lower fluoride dose. Both animal and human studies showed that, it may reduce bone mineralization and decrease the strength of bone at higher doses of fluoride. This may explain why many of the patients treated

with fluoride have an extremely low hip bone density(Table 4.1), which may result in increased fracture risk. This risk may be further enhanced once the osteogenic responses begin in the presence of calcium malabsorption, and result in skeletal bone loss. Bone biopsy in one study revealed 75 mg sodium fluoride a day for 4 years induced osteomalacia in osteoporotic patients(Riggs, B. L., Hodgson, S. F., et al, 1990). This might be due to the strong fluoride stimulation for bone formation that cause calcium deficiency and such calcium deficiency might be the possible factor for stress fractures(Lundy, M. W., Stauffer, M., et al, 1995).

4.7. Sodium monofluorophosphate preparation

Sodium monofluorophosphate is a non-toxic fluoride preparation has fewer side-effects than sodium fluoride. Sodium monofluorophosphate preparations often contained calcium to eliminate the risk of hypomineralization due to the intake of fluoride without calcium. In addition, Sodium monofluorophosphate preparations appear to be better tolerated, with a significant decrease in gastric mucosal lesions(Muller, P., Schmid, K. et al, 1992). Moreover, it has been shown that, with similar fluoride content, sodium monofluorophosphate, due to its better intestinal absorption, compared with sodium fluoride, is more effective in stimulating trabecular bone formation(Delmas, P. D., Dupuis, J., et al, 1990).

The bioavailability of fluoride in serum from oral ingestion of sodium monofluorophosphate was assessed in one study(Trautner, K. and Einwag,

J., 1987; Trautner, K. and Einwag, J., 1989). Aqueous solutions of sodium fluoride, monofluorophosphate (Na_2FPO_3, MFP) and MFP containing tablets(Caflu, Tridin) were given to fasting healthy volunteers. Serum fluoride profile and urinary fluoride output were found to be identical for all cases. On a follow-up experiment, Caflu was given together with milk, breakfast, breakfast and milk, or on a fasting stomach. The fluoride bioavailability was found to be reduced by 28% in the milk only group, 22% in the milk and breakfast group, and there was no difference between the fasting and breakfast only group. This suggested bioavailability of fluoride is greatly affected by the formation of calcium salts and prolonged stay of calcium salts in the chyma after ingestion allow fluoride to be released by digestive processes.

In a controlled study(Rizzoli, R., Chevalley, T., et al, 1995), forty-eight corticosteroid-induced osteoporosis patients were divided into two groups. Patient characteristics of mean age, year after menopause(for women) , fracture history, BMI, duration and mean daily doses of prednisone were similar. The treatment group consisted of 13 male and 12 female received sodium monofluorophosphate (26 mg fluoride) and 1000 mg calcium a day, and the control group consisted of 10 male and 13 female received only 1000 mg calcium a day, they both are followed up for 18 months. Lumbar spine BMD in the fluoride-calcium group increased by 7.8 ± 2.2 % compared with 3.6 ± 1.3 % in those given calcium after 18 months. However, the BMDs of femoral neck and midfemoral shaft were lower in the fluoride-calcium treated group compared with the group given calcium alone. The changes in

BMDs expressed as percent were -1.5 ± 1.8 % versus +0.9 ± 1.8 % for femoral neck, and -1.1 ± 1.1 % versus -0.5 ± 1.4.% for midfemoral shaft after 18 months of follow-up in the monofluorophosphate-calcium treated group and the group given calcium alone, respectively. These results indicated that the combination of sodium monofluorophosphate and calcium were more efficient than calcium alone in increasing lumbar spine BMD in patients with corticosteroids-induced osteoporosis; neither femoral neck nor femoral shaft BMD was increased.

In another prospective double-masked randomised study of 94 osteoporotic patients aged 50-70(Sebert, J. L., Richard, P., et al, 1995), patients received 26.4 mg fluoride ion (200 mg sodium monofluorophosphate) and 1000 mg calcium ion, or placebo (1000 mg calcium ion) a day for two years. Lumbar spine BMD increased by 7.1 % per year in the fluoride treatment group and 71.4 % of the treated patients showed an increase in lumbar spine BMD of more than 0.034 g / cm^2 compared with the control group. Gastric intestinal side effect was similar in the fluoride treated or control group(22 % to 18 %), but pain in the lower limbs was higher in the fluoride treated group(11 %) than in the control group(4 %). Tolerance was considered to be good and very good by more than 80 % of patients in each group.

Table 4.1 Summary from recent studies of BMD with fluoride

Investigator	Equipment	Population	NaF a day MFP a day	Site	Change in BMD (%)	Side effect Comments
(Hodsman, A. B. and Drost, D. J., 1989)	DPA	48 female age:63±10.1 year	20-60mg NaF 1g Ca 16 months	L2-L4 Forearm	+ 8.4% - 7.7%	69% F responders 21% Gastric discomfort 25% Lower leg pain 4.% Fracture
(Mamelle, N., Meunier, P. J., et al, 1988)	N/A	257 male/ female	50mg NaF 1g Ca 800IU Vitamin D_2	Spine	N/F	fell in fracture rate
(Meys, E., Terreaux-Duvert, F. et al, 1993)	QDR-1000	203 male/female Group 1:>-1.5SD Group 2< -1.5SD	1g Ca, 200mg MFP 1000 IU Calcidiol Same as above	L2-4	+12.5 % / year +29.5% / 2 year	16% gastric discomfort 8% lower leg pain
(Pouilles, J. M., Tremollieres, F., et al, 1991)	DPA	52 female age: 60±5	50 mg NaF 1g Calcium 400 IU Vitamin D_2 24 months	L2-L4 Hip	+ 5.5% / year No change	49% F responders 29% gastric discomfort 4% lower leg pain 12% withdrawn
(Rizzoli, R., Chevalley, T., et al, 1995)	QDR-1000	48 subjects on corticosteroids > 1 year	200mg MFP 1g Calcium 1g Calcium only	L2-L4 Hip(neck) Forearm L2-L4 Hip(neck) Forearm	+7.8 % / year -1.5 % / year -1.1 % / year +3.6 % / year +0.9 % / year -0.5 % / year	Dietary Ca <400 mg/day Similar to Hong Kong (Lau, E. M. and Cooper, C., 1993)

Table 4.1 (Continue)

Investigator	Equipment	Population	NaF a day MFP a day	Site	Change in BMD (%)	Side effect Comments
(Riggs, B. L., Hodgson, S. F., et al, 1990)	Unknown	202, white female Age:50-75 postmenopausal With known fracture	75 mg NaF 1.5 g calcium	LS Hip(neck) Hip(Inter)* Forearm	+8.2 % / year +1.8 % / year -1.8 % / year -1.8 % / year	Side effect 65 % for 4 year in NaF group and 26 % for 4 year in calcium group
		Length of study: 4 year	1.5g calcium	LS Hip(neck) Hip(Inter)* Forearm	+0.4 % / year -0.9 % / year -0.7 % / year -0.4 % / year	
(Thiebaud, D., Burckhardt, P. et al, 1994)	QDR-1000	16 female age: 67	20-30 mg F^- a day 1g Calcium	L2-L4 Hip(neck) Forearm	+12.0 % /2 year -0.5 % / 2 year -1.3 % / 2 year	L2-L4 + 3% /6 months
(Zerwekh, J. E., Hagler, H. K., et al, 1994)	DXA	23 male and female with one or more vertebral fracture	50 mg Slow-release NaF 50 µg Vitamin D_3 1.5g calcium	L2-L4	+8.3 % in serve osteoporotic case at start +3.4 % in mild osteoporotic case at start	Increase in Lumbar spine BMD Increase in mineral apposition rate Increase in bone fluoride contain decrease in trabecular spacing

* = Hip(intertrochanteric region)

Chapter 5 Phase II: The effects of fluoride on bone mineral density of OAD patients on steroid treatment

5.1. Objectives

To study if daily oral administration of 20 mg monofluorophosphates (plus 600 mg calcium) will increase BMDs at the hip and spine in chronic asthmatic subjects, who are on inhaled steroid therapy of 800 μg - 4000 μg per day.

5.2. Subjects and methods

5.2.1. Power of the study

In order to detect a statistical difference of 0.8 with a power of 0.75 and type I error of 5% between treatment and the control groups. The minimum number of patients required in each group is 20.

5.2.2. Subjects

Disease definition and selection criteria

Patients who fulfilled the following criteria were studied:-

a) Diagnosed to have chronic obstructive airway diseases or asthma by a qualified physician, and were taking inhaled steroids(> 800 μg / day).

b) Aged 18 years and over.

c) Have never had a history of metabolic bone disease.

Patients were recruited from the Specialist Respiratory Disease Clinic at the Prince of Wales Hospital. All eligible patients who were registered with the clinic were recruited. The trial was conducted from January 1995 to December 1995.

5.2.3. Method of randomisation

To ensure equal number of patients allocated to each treatment group. Three permuted blocks A, B and C were generated by a computing program. In brief, each block contained 40 cells(5 by 8 cells), Each participate of that group assigned a of letter F (Tridin) or P (Calcium) randomly. The order of assigning a patient to the blocks were from the left to the right and then the top to the bottom(Table 5.1). However, the distribution of age and BMI were widely scatter, since the BMDs are affected by advanced age. In order to minimise the confounding effects of age, sex and BMI on the BMDs in this phase of study, the OAD patients taking Tridin or calcium from each block were matched according to age, sex and BMI. Finally, forty one sex, age and BMI matched pairs were formed and the data of the unmatched subjects were not analysed in the study.

5.2.4. Treatment modalities

5.2.4.1. Treatment group

The treatment group was prescribed two Tridin tablets twice a day, to be taken before breakfast and going to bed. The tablets were chewed and swallowed with a glass of water. Each tablet contained the following active ingredients: L-gluatamine monofluorophosphate 134 mg, calcium D-gluconate monohydrate 500 mg, and calcium citrate tetrahydrate 500 mg, equivalent to 5 mg fluoride and 150 mg calcium. The total drug intake was thus 20 mg fluoride and 600 mg calcium per day for the treatment group.

5.2.4.2. Control group

The control group was prescribed identical tablets with similar constituents to the treatment group except for the monofluorophosphates. The frequency and mode of intake were similar to the treatment group. The total drug intake was 600 mg elemental calcium per day for the control group.

5.2.5. Bone mineral density measurements

The outcome measurements were percentage changes in bone mineral densities at the hip and spine as measured by dual X-ray densitometry (Hologic QDR 2000).

Bone mineral density was measured at the beginning of the trial and after nine months follow up. For subjects who had drug treatment less than nine months but intended to drop out of the trial, a BMD measurement was taken before they exited.

5.2.6. Routine quality control of measurement and precision on patient repositioning

The procedures have been described in sections 3.2.5.3 and 3.2.5.4.

5.2.7. Methods of monitoring drug compliance

Subjects were followed up at the respiratory clinic every 4-6 weeks. During their visit, a researcher asked them in details about the happenings of side effects and their compliances of drug intake. Ten to twenty extra tablets were prescribed at each visit and the remaining tablets that the subjects brought back were counted to monitor their compliances.

5.2.8 Statistical methods

Chi-square test and paired t-test were applied to compare lifestyle factors between the treatment and control groups at the beginning of the trial. The percentage changes in BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle between the Tridin and control group were compared by paired t-test.

Table 5.1. Permutation blocks to show the assignment of OAD patients to the Tridin or the calcium treatment groups

Block A: Pre-menopausal women on inhaled steroids

	1	2	3	4	5	6	7	8
1	P	F	P	P	F	P	F	F
2	F	F	P	F	F	P	P	P
3	P	F	F	F	F	P	P	P
4	F	F	F	F	P	P	P	P
5	P	F	F	P	F	F	P	P

Block B: Post-menopausal women on inhaled steroids

	1	2	3	4	5	6	7	8
1	F	F	F	F	F	P	P	P
2	P	P	F	P	F	P	F	F
3	F	F	P	F	P	F	P	P
4	P	F	P	F	F	P	F	P
5	F	P	F	P	P	P	F	P

Block C: Men on inhaled steroids

	1	2	3	4	5	6	7	8
1	F	F	F	P	P	F	P	P
2	P	F	F	F	F	P	F	F
3	F	P	P	P	F	P	F	F
4	P	F	F	P	F	P	P	F
5	F	F	F	P	F	P	P	P

P = Calcium F = Tridin

Assignment order: A1/1, A1/2, A1/3, A1/4, A1/5, A1/6, A1/7, A1/8, B1/1 etc.

Chapter 6 Results for phase I

6.1. Statistical power of this phase of the study

The statistical power of this phase of the study was summarised as below:

	A	B	C	D	E	F
dr	0.5	0.5	0.65	0.5	0.55	0.55
(n)	37	36	14	33	24	24
Power	0.75	0.75	0.65	0.7	0.7	0.7

A: Pre-menopausal OAD women on inhaled steroids and controls

B: Post-menopausal OAD women on inhaled steroids and controls

C: Post-menopausal OAD women not on inhaled steroids and controls

D: OAD men on inhaled steroids and controls

E: OAD men not on inhaled steroids and controls

F: OAD men and Women not on inhaled steroids and controls

n: Number of matched pairs

dr: Magnitude of difference to be detected between the two groups

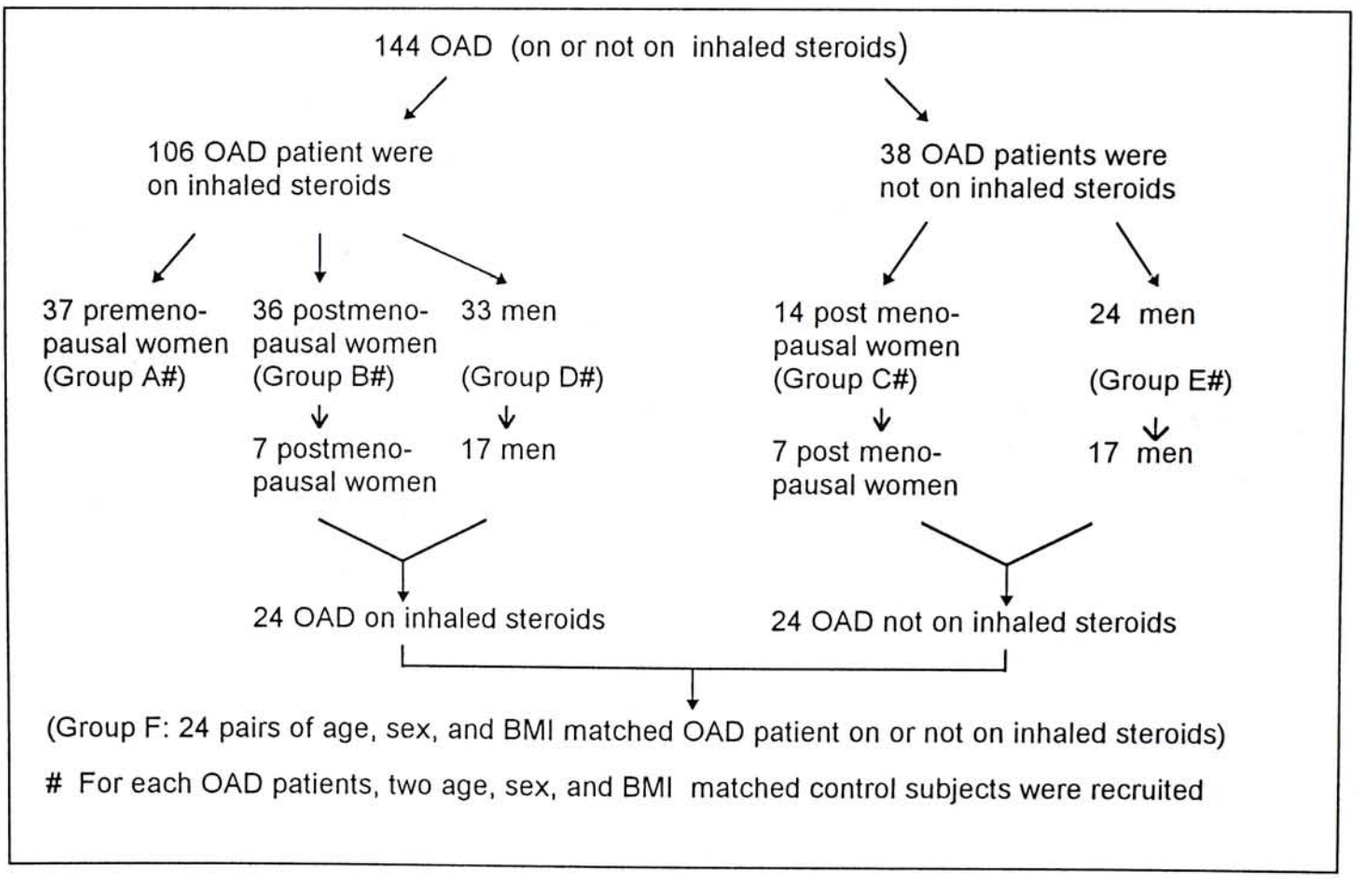
Groups A, B and D had statistical power of 0.75. 0.75 and 0.7, respectively, group C had a statistical power of 0.65, and group E and F had statistical power of 0.7. The power was affected by the sample size, the smaller the small size the lower of the power.

6.2. Clinical features of OAD subjects on inhaled steroid

One hundred and forty-four OAD men and women were recruited, of whom 106 were on inhaled steroids and 38 were not on inhaled steroids. For those 106 OAD patients on inhaled steroids: They were stratified into: Group

A consisted of 37 pre-menopausal women, group B consisted of 36 post-menopausal women and group D consisted of 33 men, among these OAD patients on inhaled steroid, seven, nine and ten had used oral steroid in the past. For those 38 OAD patients not on inhaled steroids, they were stratified into: Group C consisted of 14 post-menopausal women and group E consisted of 24 men. Group F consisted of 24 age, sex and BMI matched pairs of OAD patients on or not on inhaled steroids(Chart 6.1).

Chart 6.1 Stratification for OAD patients



For each OAD patient, their BMDs and body compositions were compared with two age, and BMI matched normal control subjects. There

were significant differences among some of the demographic and baseline characteristics as set out in table 6.1a to 6.1f,

Smokers and drinkers were predominately found among older male patients and their control subjects with or without the use of inhaled steroids(Table 6.1d-e). Compared with the normal control subjects, there were statistically significant more smokers and drinkers among the OAD patients. Moreover, exposure to cigarette smoke measured as pack years were significantly greater in the OAD patients than in their matched control subjects.

Daily dietary calcium intake among the whole study groups and normal control subjects ranged from 197 to 324 mg / day(Table 6.1c). There were no statistical differences in most groups except the OAD post-menopausal group, where the calcium intake in the control group(324 ± 69 mg / day) was higher than the patients(197 ± 125 mg / day) ($p<0.05$)(Table 6.1.c).

The age of menarche in the pre-menopausal women(Table 6.1a) was 14 years old compared to 16 to 17 years old in the post-menopausal groups(Table 6.1b-c). The age of menopause among post-menopausal women was around forty-six to forty-eight years old(Table 6.1b-c).

Past history of using oral contraceptive was significantly higher in the OAD pre-menopausal women when compared with the pre-menopausal control subjects(Table 6.1a), and there were fewer oral contraceptive users among post-menopausal women control subjects(table 6.1b-c).

6.3. Anthropometric measurements and bone mineral density

The body compositions and bone mineral densities of the five study groups were presented in table 6.2a-6.2e, and the differences in bone mineral density between the OAD patients on inhaled steroids and the OAD patient not on inhaled steroid were presented in table 6.2f.

Significant differences in body height($p<0.01$), body mass index($p<0.001$), fat mass($p<0.01$) and percentage of body fat(0.001) between the pre-menopausal OAD women on inhaled steroids and their controls were found(table 6.2a). The BMD of the total body($p<0.05$) was significant lower in pre-menopausal OAD women taking inhaled steroid. However, this significance was removed after adjustment for confounding factors(Table 6.3.a).

In the group of post-menopausal OAD women on inhaled steroids(table 6.2b), significant differences in body mass index($p<0.05$) and fat mass($p<0.05$) were found. The BMD at the lumbar spine(L1-L4)($p<0.01$) was significant lower in postmenopausal OAD women taking inhaled steroids than their matched controls. However, this significance was removed after adjustment of confounding factors(Table 6.3b)

In the group of post-menopausal OAD women not on inhaled steroids(table 6.2c), no significant differences were found for any of the anthropometric measurements and bone mineral densities.

In the group of OAD men on inhaled steroids(table 6.2d), significant difference in body weight was noted($p<0.05$). The BMDs of the lumbar

spine($p<0.01$), femoral neck($p<0.05$), intertrochanteric region($p<0.01$) and Ward's triangle($p<0.05$) of the patients were also significantly lower than those of the controls. However, after adjustment of confounding factors, none of the above BMDs remained statistically significant.

In the group of OAD men not on inhaled steroids(table 6.2e), significant differences between the treatment and control groups were found for body weight, body height and lean body mass($p<0.05$). The BMDs of the total body($p<0.05$), lumbar spine($p<0.05$), femoral neck($p<0.001$), intertrochanteric region($p<0.001$) and Ward's triangle($p<0.01$) were significantly lower among the patient group. After adjustment for confounding factors, BMDs of the femoral neck, intertrochanteric region and Ward's triangle remained statistically significant(Sig of $F < 0.05$)(Table 6.3e.).

Comparing the OAD patients (men and women) on inhaled steroids and those not on inhaled steroids, no significant difference was found for all the anthropometic measurements taken between the two groups. Only the BMD of lumbar spine was found significant lower in the group taking inhaled steroids($p<0.05$)(Table 6.2.f). After adjustment for confounding factors, the lumbar spine BMD remained statistically significant(Sig of $F <0.05$).

The fat mass was similar between the premenopausal and postmenopausal women on inhaled steroids(23 ± 9 kg and 25 ± 8 kg, respectively)(Table 6.2a-b), and their fat masses were statistical significantly higher than their age matched normal control subjects(Table 6.2a, $p<0.05$; table 6.2b, $p<0.01$). However, the OAD women not on inhaled steroids did

not show increased body fat mass compared with their age matched controls(table 6.2c).

For the OAD men, there were no statistically significant differences in fat mass and percentage of body fat among subjects taking inhaled steroids (table 6.2d), those not taking inhaled steroids(Table 6.2e) and their age and BMI matched control subjects.

The lean body mass was not significantly difference between most of the patient groups and their age matched control, except for the OAD men not on inhaled steroids who had lower lean body mass than their normal control subjects(Table 6.2.e.).

In this study, the men patients had higher lean body mass and lower fat mass than the women patients(Table 6.2.a-c). The older patients(Table 6.2d-f) had lower fat mass than the young patients(Table 6.2.a.). The lean body masses among women patients were similar(Table 6.2.a-c.).

The overall BMDs of all the case and control subjects decrease with advancing aging. The women had lower BMD than the men, and the young women had higher BMDs than the old women. Also, the OAD men had lower BMDs than their control subjects.

6.4. Analysis of covariance for BMDs differences

The analysis of covariance for BMDs differences between the OAD patients and their matched normal controls adjusted for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise per week were performed and the results were shown in tables 6.3a to 6.3f.

In table 6.3a, the adjusted means of BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle of the premenopausal women OAD patients on inhaled steroids were similar to that of their age and BMI matched normal controls.

In table 6.3b, the adjusted means of BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle of the postmenopausal women on inhaled steroids were lower than those of the age and BMI matched controls. However, the differences were not statistically significant.

In table 6.3c, the adjusted means of BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle of the postmenopausal women who were not on inhaled steroids were lower than that of the age and BMI matched controls. However, the differences were not statistically significant.

In table 6.3d, the adjusted means of BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle of the OAD

men on inhaled steroids were lower than that of the age and BMI matched controls. However, their differences were not statistically significant.

In table 6.3e, the adjusted means of BMDs of the femoral neck, intertrochanteric region and Ward's triangle of the OAD men who were not on inhaled steroids were statistically significantly lower than that of their age and BMI matched controls(Sig of Fs <0.05). However, the differences of the adjusted means of BMDs of the total body and lumbar spine were not statistically significant.

In table 6.3f, the adjusted means of BMDs of the lumbar spine of the OAD men and women who were taking inhaled steroids were statistically significant lower than those of the OAD men and women who were not taking inhaled steroids(Sig of F <0.05). However, the differences of the adjusted means of BMDs of the femoral neck, intertrochanteric region and Ward's triangle were not statistically significant.

6.5. Multiple regression

Multiple regression was conducted to study the relative importance of the following factors in determining the BMD of the OAD patients: age, sex, duration of asthma, BMI, daily dietary calcium intake, cumulative dose of oral steroids, cumulative dose of inhaled steroids, current dose of inhaled steroids, and length of inhaled steroids use.

The results of multiple regression against various variables of all OAD patients on inhaled steroids and the regression coefficients of the total BMD are shown in tables 6.3a to 6.3f.

Age, sex, duration of asthma, BMI, daily dietary calcium intake, cumulative dose of oral steroids, cumulative dose of inhaled steroids, current dose of inhaled steroids and length of inhaled steroids were used as the independent variables, with lumbar spine BMD, total body BMD, femoral neck BMD, total body BMD, femoral BMD, hip intertrochanteric BMD and Ward's triangle BMD as the dependent variables.

Age was the only factor negatively significant associated with lumbar spine BMD, femoral neck BMD, intertrochanteric and Ward's triangle BMD. In addition oral steroids usage was negatively associated with the femoral neck BMD, whilst BMI was positively associated with the intertrochanteric BMD.

6.6 Correlation

There were significant correlations among some of the anthropometric indices such as FEV1, height, lean body mass, body weight, fat content, past intake of oral steroids and BMD as set out in Appendix Table A.4.

Bone mineral density decreased with increasing age(from r^2 = -0.800 for Ward's triangle to r^2 = -0.450 for total body BMD), duration of asthma, alcohol intake, age of menarche, and intake of oral steroids.

Bone mineral density increased with increasing body weight, BMI, fat mass, lean mass, and lung function.

Table 6.1a: Demographic and baseline characteristics of the premenopausal OAD female patients on inhaled steroids and normal control subjects (mean ± SD)

	OAD on Inhaled steroids 37	Normal Control 74
Age	36 ± 7	36 ± 7
Age of menarche	14 ± 2	13 ± 1
Age of menopause	N/A	N/A
Cumulative dose of oral steroids (mg)	95 ± 255	N/A
Oral steroid user (%)		
never	81	100
ever	19	0
Cumulative dose of inhaled steroids (mg)	389 ± 180	N/A
Duration of use of inhaled steroids (week)	45 ± 17	N/A
Current dose of inhaled steroids (μg per day)	1411 ± 713	N/A
Average daily dose of inhaled steroid (μg)	1310 ± 569	N/A
Daily dietary calcium (mg)	216 ± 85	230 ± 73
Years of drinking among drinker(year)	4 ± 0	2 ± 0
Alcohol drinking (%)		
never	97	99
ever	3	1
Alcohol intake among drinker (g/week)	52 ± 0	13 ± 0
Cigarette smoking (%)		
never	97	95
ever	3	5
Years of smoking among smoker	4 ± 0	7 ± 5
Cigarette pack year among smoker	1 ± 0	2 ± 1
Load bearing exercise (hours/week)	0 ± 1	1 ± 1
Ever use oral contraceptives (%)		
never	60	55
ever	40	45
Months of oral contraceptive use among oral contraceptive user	27 ± 33	60 ± 61*

Paired t-tests:

* $p < 0.05$

Table 6.1b Demographic and baseline characteristics of the postmenopausal OAD female patients on inhaled steroids and normal control subjects (mean ± SD)

	OAD on Inhaled steroids 36	Normal Control 72
Age	64 ± 9	64 ± 9
Age of menarche	16 ± 2	16 ± 2
Age of menopause	48 ± 5	49 ± 4
Cumulative dose of oral steroids (mg)	144 ± 305	N/A
Oral steroid user (%)		
never	75	100
ever	25	0
Cumulative dose of inhaled steroids (mg)	592 ± 221	N/A
Duration of use of inhaled steroids (week)	42 ± 13	N/A
Current dose of inhaled steroids (μg per day)	1522 ± 508	N/A
Average daily dose of inhaled steroid (μg)	1446 ± 425	N/A
Daily dietary calcium (mg)	238 ± 124	275 ± 77
Years of drinking among alcohol drinker(year)	3 ± 0	5 ± 0
Alcohol drinking (%)		
never	89	99††
ever	11	1
Alcohol intake among alcohol drinker (g/week)	54 ± 0	816 ± 0
Cigarette smoking (%)		
never	67	93†††
ever	33	7
Years of smoking among cigarette smoker	17 ± 12	10 ± 10
Cigarette pack year among cigarette smoker	8 ± 7	1 ± 1
Load bearing exercise (hour/week)	0 ± 1	2 ± 2**
Ever use contraceptives (%)		
never	14	26
ever	86	74
Months of oral contraceptive use among oral contraceptive user	13 ± 16	9 ± 10

Paired t-tests:

** $p < 0.01$

Chi-square test:

†† $p<0.01$

††† $p<0.001$

Table 6.1c Demographic and baseline characteristics of the postmenopausal OAD female patients not on inhaled steroids and normal control subjects (mean ± SD)

	OAD female patient not on inhaled steroids	Normal Control
	14	28
Age	75 ± 5	75 ± 5
Age of menarche	17 ± 3	16 ± 1
Age of menopause	46 ± 5	50 ± 5
Intake of oral steroids (mg)	N/A	N/A
Oral steroid user (%)		
never	100	100
ever	0	0
Daily dietary calcium (mg)	197 ± 126	324 ± 69*
Years of drinking among drinker	2 ± 1	0 ± 0
Alcohol drinking (%)		
never	86	100†
ever	14	0
Alcohol intake among drinker (g/week)	55 ± 51	0 ± 0
Cigarette smoking (%)		
never	14	64†††
ever	86	36
Years of smoking among cigarette smoker	24 ± 13	20 ± 11
Cigarette pack year among cigarette smoker	7 ± 6	10 ± 9
Load bearing exercise (hour/week)	0 ± 0	0 ± 0
Ever use contraceptives (%)		
never	14	7
ever	86	93
Months of contraceptive use among oral contraceptive user	144 ± 0	12 ± 0

Paired t-tests

* $p < 0.05$

Chi-square test:

† $p<0.05$

††† $p<0.001$

Table 6.1d Demographic and baseline characteristics of the OAD male patients on inhaled steroids and normal control subjects (mean ± SD)

	OAD male patient on inhaled steroids 33	Normal Control 66
Age	63 ± 9	64 ± 9
Oral steroid user (%)		
never	70	100
ever	30	0
Cumulative dose of oral steroids (mg)	203 ± 433	N/A
Cumulative dose of inhaled steroids (mg)	376 ± 153	N/A
Duration of use of inhaled steroids (week)	40 ± 11	N/A
Current dose of inhaled steroids (μg per day)	1333 ± 502	N/A
Average daily dose of inhaled steroid (μg)	1374 ± 445	N/A
Daily dietary calcium (mg)	201 ± 98	254 ± 81*
Alcohol drinking (%)		
never	42	61†
ever	58	39
Years of drinking among alcohol drinker	25 ± 14	20 ± 13
Alcohol intake among alcohol drinker(g/week)	81 ± 57	867 ± 635*
Cigarette smoking (%)		
never	18	44†††
ever	82	56
Years of smoking among cigarette smoker	37 ± 10	27 ± 19
Cigarette pack year among cigarette smoker	32 ± 26	19 ± 17*
Load bearing exercise (hour/week)	0 ± 0	2 ± 3**

Paired t-tests:

* $p < 0.05$
** $p < 0.01$

Chi-square test

† $p<0.05$
††† $p<0.001$

Table 6.1e Demographic and baseline characteristics of the OAD male patients not on inhaled steroids and normal control subjects (mean ± SD)

	OAD male patients not on inhaled steroids 24	Normal Control 48
Age	70 ± 7	71 ± 7
Intake of oral steroids (mg)	N/A	N/A
Oral steroid user (%)		
never	100	100
ever	0	0
Daily dietary calcium (mg)	211 ± 118	255 ± 82*
Alcohol drinking (%)		
never	63	63
ever	37	37
Years of drinking among alcohol drinker	53 ± 11	24 ± 5*
Alcohol intake among alcohol drinker(g/week)	96 ± 101	3736 ± 5012
Cigarette smoking (%)		
never	0	33†††
ever	100	67
Years of smoking among cigarette smoker	50 ± 13	30 ± 16***
Cigarette pack year among cigarette smoker	51 ± 33	26 ± 19**
Load bearing exercise (hour/week)	0 ± 1	2 ± 3*

Paired t-tests

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Chi-square test

††† $p<0.001$

Table 6.1f Demographic and baseline characteristics of the OAD patients on inhaled steroids and OAD patients not on inhaled steroids(mean ± SD)

	OAD patients on inhaled steroids	OAD patients not on inhaled steroids
	24	24
Sex (female/male)	7/17	7/17
Age	69 ± 5	70 ± 6
Age of menarche among female (year)	16 ± 3	17 ±3
Age of menopause among female (year)	46 ±5.1	46 ± 4
Peak flow rate (ml/min)	220 ±87.0	262 ± 104
FVC	2 ± 1	2 ± 1
FEV1	1 ± 1	1 ± 1
Duration of OAD (year)	15 ± 17	7 ± 6*
Oral steroid user (%)		
never	67	100†††
ever	33	0
Cumulative dose of oral steroids (mg)	101 ± 87	N/A
Cumulative dose of inhaled steroids (mg)	416 ± 191	N/A
Duration of use of inhaled steroids (week)	42 ± 12	N/A
Current dose of inhaled steroids (μg per day)	1375 ± 535	N/A
Average daily dose of inhaled steroid (μg)	1410 ± 492	N/A
Daily dietary calcium (mg)	214 ± 128	194 ± 95
Alcohol drinking (%)		
never	67	71
ever	33	29
Years of drinking among alcohol drinker	21 ± 15	27 ± 22
Alcohol intake among alcohol drinker(g/week)	200 ± 150	213 ± 145
Cigarette smoking (%)		
never	25	0†††
ever	75	100
Years of smoking among cigarette smoker	35 ± 12	40 ± 16
Cigarette pack year among cigarette smoker	39 ± 24	34 ± 24
Load bearing exercise (hour/week)	0 ± 0	0 ± 1
Ever use contraceptives %		
never	100	100
ever	0	0

Paired t-tests: Chi-square test

* $p < 0.05$ ††† $p<0.001$

Table 6.2a: Anthropometric measurements and bone mineral density for premenopausal OAD female patients on inhaled steroids and control subjects(mean ± SD)

	OAD on inhaled steroids	Normal control
	37	74
Body measurement		
Weight (kg)	58 ± 9	57 ± 7
Height (M)	1.5 ± 0.1	1.6 ± 0**
BMI (kg/H^2)	25 ± 3.6	23 ± 3***
Fat mass (kg)	23 ± 9	20 ± 5*
% of body fat (kg)	39 ± 5	34 ± 6***
Lean body mass (kg)	34 ± 4	35 ± 3
Bone mineral density (gm/cm^2)		
Total body	1.012 ± 0.07	1.046 ± 0.035*
Spine (L1-L4)	0.949 ± 0.11	0.984 ± 0.063
Femoral neck	0.793 ± 0.08	0.788 ± 0.067
Intertrochanteric	1.067 ± 0.112	1.066 ± 0.095
Ward's triangle	0.725 ± 0.118	0.718 ± 0.108

Paired t-tests:

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 6.2b: Anthropometric measurements and bone mineral density for postmenopausal OAD female patients on inhaled steroids and control subjects(mean ± SD)

	OAD on steroids	Normal Control
n=	36	72
Body measurement		
Weight (kg)	56 ± 10	53 ± 10
Height (M)	1.5 ± 10	1.5 ± 0
BMI (kg/H^2)	25 ± 4	24 ± 3
Fat mass (kg)	25 ± 8	21 ± 6*
% of body fat (kg)	42 ± 9	37 ± 6
Lean body mass (kg)	33 ± 3	32 ± 3
Bone mineral density (gm/cm^2)		
Total body	0.864 ± 0.079	0.885 ± 0.094
Spine (L1-L4)	0.699 ± 0.133	0.761 ± 0.132**
Femoral neck	0.580 ± 0.134	0.611 ± 0.091
Intertrochanteric	0.804 ± 0.174	0.826 ± 0.136
Ward's triangle	0.402 ± 0.151	0.441 ± 0.118

Paired t-tests:

* $p < 0.05$

** $p < 0.01$

Table 6.2c: Anthropometric measurements and bone mineral density for postmenopausal OAD female patients not on inhaled steroids and control subjects(mean ± SD)

	OAD Patient not on inhaled steroids	Normal Control
n=	14	28
Body measurement		
Weight (kg)	46 ± 9	48 ± 7
Height (M)	1.5 ± 0	1.5 ± 0
BMI (kg/H^2)	21 ± 4	22 ± 3
Fat mass (kg)	15 ± 7	16 ± 6
% of body fat (kg)	31 ± 12	33 ± 8
Lean body mass (kg)	30 ± 3	31 ± 2
Bone mineral density (gm/cm^2)		
Total body	0.824 ± 0.066	0.827 ± 0.062
Spine (L1-L4)	0.639 ± 0.088	0.683 ± 0.083
Femoral neck	0.466 ± 0.182	0.534 ± 0.049
Intertrochanteric	0.605 ± 0.223	0.738 ± 0.095
Ward's triangle	0.310 ± 0.154	0.339 ± 0.068

Table 6.2d: Anthropometric measurements and bone mineral density for OAD male patients on inhaled steroids and control subjects(mean ± SD)

	OAD on inhaled steroids	Normal control
n=	33	66
Body measurement		
Weight (kg)	57 ± 9	61 ± 6*
Height (M)	1.6 ± 0	1.6 ± 0
BMI (kg/H^2)	22 ± 3	23 ± 2
Fat mass (kg)	14 ± 6	15 ± 6
% of body fat (kg)	25 ± 6	23 ± 5
Lean body mass (kg)	42 ± 7	44 ± 6
Bone mineral density (gm/cm^2)		
Total body	0.995 ± 0.095	1.035 ± 0.058
Spine (L1-L4)	0.819 ± 0.131	0.917 ± 0.103**
Femoral neck	0.637 ± 0.105	0.702 ± 0.080*
Intertrochanteric	0.880 ± 0.160	0.991 ± 0.105**
Ward's triangle	0.448 ± 0.118	0.510 ± 0.091*

Paired t-tests:

* $p < 0.05$

** $p < 0.01$

Table 6.2e: Anthropometric measurements and bone mineral density for OAD male patients not on inhaled steroids and control subjects(mean ± SD)

	OAD patient not on inhaled steroids	Normal Control
n=	24	48
Body measurement		
Weight (kg)	56 ± 10	60 ± 8*
Height (M)	1.6 ± 0	1.6 ± 0
BMI (kg/H^2)	22 ± 4	23 ± 3
Fat mass (kg)	13 ± 7	15 ± 5
% of body fat (kg)	22 ± 9	23 ± 5
Lean body mass (kg)	41 ± 5	43 ± 4*
Bone mineral density (gm/cm^2)		
Total body	0.983 ± 0.065	1.019 ± 0.065*
Spine (L1-L4)	0.868 ± 0.114	0.931 ± 0.106*
Femoral neck	0.591 ± 0.078	0.683 ± 0.085***
Intertrochanteric	0.840 ± 0.125	0.980 ± 0.106***
Ward's triangle	0.382 ± 0.083	0.474 ± 0.100**

Paired t-tests:

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 6.2f: Anthropometric measurements and bone mineral density for OAD patients on inhaled steroids and OAD patients not on inhaled steroids(mean ± SD)

	OAD patients on inhaled steroids 24	OAD patients not on inhaled steroids 24
Female / male	7/17	7/17
Body measurement		
Weight (kg)	53 ± 7	53 ± 9
Height (M)	1.6 ± 0	1.6 ± 0
BMI (kg/H^2)	22 ± 3	22 ± 4
Fat mass (kg)	16 ± 6	16 ± 7
% of body fat (kg)	28 ± 10	28 ± 10
Lean body mass (kg)	39 ± 5	39 ± 6
Bone mineral density (gm/cm^2)		
Total body	0.923 ± 0.103	0.937 ± 0.080
Spine (L1-L4)	0.734 ± 0.142	0.800 ± 0.136*
Femoral neck	0.570 ± 0.125	0.584 ± 0.079
Intertrochanteric	0.800 ± 0.187	0.794 ± 0.107
Ward's triangle	0.369 ± 0.130	0.392 ± 0.085

Paired t-tests:

* $p < 0.05$

Table 6.3a. Analysis of covariance results for BMDs differences between OAD premenopausal women on inhaled steroids and matched normal controls adjusting for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body	Within + residual	0.42	91	0.00		
	Regression	0.03	6	0.00	1.04	0.400
	OAD/Normal control	0.02	1	0.02	3.56	0.060
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	1.012	1.013	1.012		
	Normal control	1.045	1.044	1.045		
Lumbar spine	Within + residual	0.96	103	0.01		
	Regression	0.13	6	0.02	2.25	0.040
	OAD/Normal control	0.03	1	0.03	3.24	0.075
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.949	0.949	0.949		
	Normal control	0.984	0.985	0.984		
Femoral neck	Within + residual	1.43	103	0.01		
	Regression	0.17	6	0.03	2.09	0.061
	OAD/Normal control	0.00	1	0.00	0.06	0.803
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.793	0.788	0.793		
	Normal control	0.776	0.781	0.776		
Intertrochanteric	Within + residual	1.43	102	0.01		
	Regression	0.25	6	0.04	2.92	0.011
	OAD/Normal control	0.00	1	0.00	0.11	0.746
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	1.067	1.062	1.067		
	Normal control	1.065	1.070	1.065		
Ward's triangle	Within + residual	1.45	102	0.01		
	Regression	0.16	6	0.03	1.82	0.102
	OAD/Normal control	0.00	1	0.00	0.35	0.556
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.725	0.719	0.725		
	Normal control	0.728	0.734	0.728		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.3b. Analysis of covariance results for BMDs differences between OAD postmenopausal women on inhaled steroids and matched normal controls adjusting for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body BMD	Within + residual	0.78	87	0.01		
	Regression	0.17	6	0.03	3.15	0.008
	OAD/Normal control	0.01	1	0.01	0.78	0.380
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	COAD	0.864	0.868	0.864		
	Normal control	0.894	0.890	0.894		
Lumbar spine	Within + residual	1.62	100	0.02		
	Regression	0.76	6	0.13	7.86	0.000
	COAD/Normal control	0.06	1	0.06	3.72	0.057
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.699	0.702	0.699		
	Normal control	0.761	0.757	0.761		
Femoral neck	Within + residual	0.89	100	0.01		
	Regression	0.63	6	0.10	11.71	0.000
	OAD/Normal control	0.01	1	0.01	1.16	0.284
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.580	0.584	0.580		
	Normal control	0.611	0.607	0.611		
Intertrochanteric	Within + residual	2.11	100	0.02		
	Regression	1.12	6	0.19	8.82	0.000
	OAD/Normal control	0.00	1	0.00	0.19	0.661
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.804	0.808	0.804		
	Normal control	0.826	0.822	0.826		
Ward's triangle	Within + residual	1.43	100	0.01		
	Regression	0.78	6	0.13	9.09	0.000
	OAD/Normal control	0.01	1	0.01	0.41	0.524
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.402	0.413	0.402		
	Normal control	0.441	0.430	0.441		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.3c. Analysis of covariance results for BMDs differences between OAD postmenopausal women not on inhaled steroids and matched normal controls adjusting for body height, body weight, cigarette pack year, alcohol intake per week, and dietary calcium intake per day

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body BMD	Within + residual	0.20	35	0.01		
	Regression	0.04	5	0.01	1.35	0.266
	OAD/Normal control	0.00	1	0.00	0.65	0.427
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.824	0.812	0.824		
	Normal control	0.827	0.839	0.827		
Lumbar spine	Within + residual	0.47	35	0.01		
	Regression	0.09	5	0.02	1.42	0.243
	OAD/Normal control	0.01	1	0.01	1.00	0.325
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.639	0.636	0.639		
	Normal control	0.683	0.686	0.683		
Femoral neck	Within + residual	0.46	35	0.01		
	Regression	0.12	5	0.02	1.83	0.132
	OAD/Normal control	0.02	1	0.02	1.79	0.190
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.466	0.466	0.466		
	Normal control	0.534	0.533	0.534		
Intertrochanteric	Within + residual	0.36	34	0.01		
	Regression	0.32	5	0.06	5.99	0.000
	OAD/Normal control	0.02	1	0.02	2.23	0.145
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.652	0.661	0.652		
	Normal control	0.738	0.729	0.738		
Ward's triangle	Within + residual	0.26	34	0.01		
	Regression	0.12	5	0.02	3.18	0.018
	OAD/Normal control	0.00	1	0.00	0.49	0.490
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.333	0.323	0.333		
	Normal control	0.339	0.350	0.339		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.3d. Analysis of covariance results for BMDs differences between OAD men on inhaled steroids and matched normal controls adjusting for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body BMD	Within + residual	0.44	79	0.01		
	Regression	0.15	6	0.02	4.33	0.001
	OAD/Normal control	0.00	1	0.00	0.10	0.752
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	COAD	0.995	1.010	0.955		
	Normal control	1.031	1.016	1.031		
Lumbar spine	Within + residual	1.33	89	0.01		
	Regression	0.50	6	0.08	5.63	0.000
	COAD/Normal control	0.03	1	0.03	1.88	0.174
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.819	0.845	0.819		
	Normal control	0.913	0.887	0.913		
Femoral neck	Within + residual	0.76	89	0.01		
	Regression	0.41	6	0.07	8.06	0.000
	OAD/Normal control	0.00	1	0.00	0.47	0.494
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.637	0.662	0.637		
	Normal control	0.703	0.678	0.703		
Intertrochanteric	Within + residual	1.27	89	0.01		
	Regression	0.78	6	0.13	9.13	0.000
	OAD/Normal control	0.03	1	0.03	2.29	0.134
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.880	0.913	0.880		
	Normal control	0.991	0.958	0.991		
Ward's triangle	Within + residual	1.00	89	0.01		
	Regression	0.39	6	0.07	5.81	0.000
	OAD/Normal control	0.00	1	0.00	0.01	0.914
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.448	0.477	0.448		
	Normal control	0.509	0.480	0.509		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.3e. Analysis of covariance results for BMDs differences between OAD men not on inhaled steroids and matched normal controls adjusting for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body BMD	Within + residual	0.34	65	0.01		
	Regression	0.09	6	0.01	2.77	0.018
	OAD/Normal control	0.01	1	0.01	2.32	0.133
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	COAD	0.983	0.984	0.983		
	Normal control	1.018	1.017	1.018		
Lumbar spine	Within + residual	1.17	65	0.02		
	Regression	0.15	6	0.03	1.41	0.226
	COAD/Normal control	0.04	1	0.04	2.14	0.148
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.868	0.872	0.868		
	Normal control	0.936	0.932	0.936		
Femoral neck	Within + residual	0.50	65	0.01		
	Regression	0.20	6	0.03	4.43	0.001
	OAD/Normal control	0.05	1	0.05	6.03	0.017
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.590	0.604	0.590		
	Normal control	0.682	0.669	0.682		
Intertrochanteric	Within + residual	0.85	65	0.01		
	Regression	0.42	6	0.07	5.41	0.000
	OAD/Normal control	0.13	1	0.13	9.69	0.003
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.840	0.856	0.840		
	Normal control	0.978	0.963	0.978		
Ward's triangle	Within + residual	0.69	65	0.01		
	Regression	0.14	6	0.02	2.22	0.052
	OAD/Normal control	0.08	1	0.08	7.84	0.007
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.382	0.384	0.382		
	Normal control	0.474	0.472	0.474		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.3f. Analysis of covariance results for BMDs differences between OAD men and women on inhaled steroids and OAD men and women not on inhaled steroids adjusting for body height, body weight, cigarette pack year, alcohol intake per week, dietary calcium intake per day and load bearing exercise

BMD	Source of variation	Sum of square	DF	MS	F	Sig of F
Total body BMD	Within + residual	0.17	25	0.01		
	Regression	0.09	6	0.01	2.13	0.085
	OAD/Normal control	0.00	1	0.01	0.73	0.402
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	COAD	0.931	0.916	0.931		
	Normal control	0.931	0.947	0.931		
Lumbar spine	Within + residual	0.38	30	0.01		
	Regression	0.18	6	0.03	2.43	0.049
	COAD/Normal control	0.05	1	0.04	4.27	0.048
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.753	0.733	0.753		
	Normal control	0.801	0.821	0.801		
Femoral neck	Within + residual	0.16	29	0.01		
	Regression	0.12	6	0.02	3.78	0.007
	OAD/Normal control	0.01	1	0.01	1.82	0.188
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.550	0.548	0.550		
	Normal control	0.585	0.586	0.585		
Intertrochanteric	Within + residual	0.29	29	0.01		
	Regression	0.40	6	0.07	6.70	0.000
	OAD/Normal control	0.01	1	0.01	0.67	0.419
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.786	0.775	0.786		
	Normal control	0.794	0.806	0.794		
Ward's triangle	Within + residual	0.22	29	0.01		
	Regression	0.06	6	0.01	1.22	0.355
	OAD/Normal control	0.01	1	0.01	0.70	0.411
	Adjusted and estimated means					
		Obs. mean	Adj. mean	Est. mean		
	OAD	0.356	0.358	0.356		
	Normal control	0.386	0.385	0.386		

Obs mean = observed mean
Adj. mean = adjusted mean
Est. mean = estimated mean

Table 6.4a. Multiple regression of total body BMD against various variables in all OAD patients on inhaled steroids

Independent variable	B	SE B	p-value
Age (year)	$-4.6e^{-03}$	$2.3e^{-03}$	0.11
Sex (male/female)	$-1.1e^{-01}$	$8.6e^{-02}$	0.24
Duration of Asthma (year)	$-7.8e^{0}$	$2.2e^{-03}$	0.73
BMI (kg/M^2)	$-1.5e^{-03}$	$9.9e^{-03}$	0.89
Daily dietary calcium intake (mg)	$1.2e^{-04}$	$3.6e^{-04}$	0.75
Cumulative dose of oral steroids (mg)	$-7.2e^{-06}$	$6.1e^{-04}$	0.99
Cumulative dose of inhaled steroids (mg)	$-3.3e^{-07}$	$2.8e^{-06}$	0.91
Current dose of inhaled steroids (μg per day)	$-4.5e^{-06}$	$1.1e^{-04}$	0.97
Length of inhaled steroids use (week)	$8.9e^{-04}$	$4.4e^{-03}$	0.85
Constant	1.4		

R^2 =0.52, p=0.80

Table 6.4b Multiple regression of lumbar spine(L1-L4) BMD against various variables in all OAD patients on inhaled steroids

Independent variable	B	SE B	p-value
Age (year)	$-7.3e^{-03}$	$1.8e^{-03}$	0.00
Sex (male/female)	$-1.4e^{-01}$	$6.5e^{-02}$	0.05
Duration of Asthma (year)	$-1.4e^{-03}$	$1.6e^{-03}$	0.39
BMI (kg/M^2)	$8.4e^{-03}$	$7.6e^{-03}$	0.27
Daily dietary calcium intake (mg)	$6.6e^{-05}$	$2.7e^{-04}$	0.81
Cumulative dose of oral steroids (mg)	$-6.9e^{-04}$	$4.7e^{-04}$	0.16
Cumulative dose of inhaled steroids (mg)	$-2.7e^{-07}$	$2.1e^{-06}$	0.90
Current dose of inhaled steroids (μg per day)	$3.4e^{-05}$	$8.0e^{-05}$	0.68
Length of inhaled steroids use (week)	$2.9e^{-03}$	$3.4e^{-03}$	0.41
Constant	1.2		

R^2=0.62, p=0.03

Table 6.4c. Multiple regression of femoral neck BMD against various variables in all OAD patients on inhaled steroids

Independent variable	B	SE B	p-value
Age (year)	$-6.4e^{-03}$	$1.3e^{-3}$	0.00
Sex (male/female)	$-7.6e^{-02}$	$4.7e^{-2}$	0.13
Duration of Asthma (year)	$-1.3e^{-03}$	$1.2e^{-3}$	0.30
BMI (kg/M^2)	$8.8e^{-03}$	$5.5e-^{3}$	0.13
Daily dietary calcium intake (mg)	$-2.1e-^{04}$	$2.0e^{-04}$	0.31
Cumulative dose of oral steroids (mg)	$-9.4e-^{04}$	$3.4e^{-04}$	0.01
Cumulative dose of inhaled steroids (mg)	$7.9e-^{07}$	$1.5e^{-06}$	0.61
Current dose of inhaled steroids (μg per day)	$2.2e-^{05}$	$5.8e^{-05}$	0.71
Length of inhaled steroids use (week)	$9.9e-^{04}$	$2.4e^{-3}$	0.69
Constant	1.0		

$R^2 = 0.74$, $p = 0.00$

Table 6.4d. Multiple regression of hip intertrochanteric region BMD against various variables in all OAD patients on inhaled steroids

Independent variable	B	SE B	p-value
Age (year)	$-8.0e^{-03}$	$1.9e^{-03}$	0.00
Sex (male/female)	$-1.3e^{-01}$	$7.1e^{-02}$	0.10
Duration of Asthma (year)	$-1.1e^{-03}$	$1.8e^{-03}$	0.56
BMI (kg/M^2)	$1.8e^{-02}$	$8.2e^{-03}$	0.04
Daily dietary calcium intake (mg)	$-1.6e^{-04}$	$2.9e^{-04}$	0.58
Cumulative dose of oral steroids (mg)	$-8.7e^{-04}$	$5.1e^{-04}$	0.10
Cumulative dose of inhaled steroids (mg)	$1.3e^{-06}$	$2.3e^{-06}$	0.58
Current dose of inhaled steroids (μg per day)	$4.2e^{-06}$	$8.7e^{-05}$	0.96
Length of inhaled steroids use (week)	$1.4e^{-03}$	$3.7e^{-03}$	0.70
Constant	1.1		

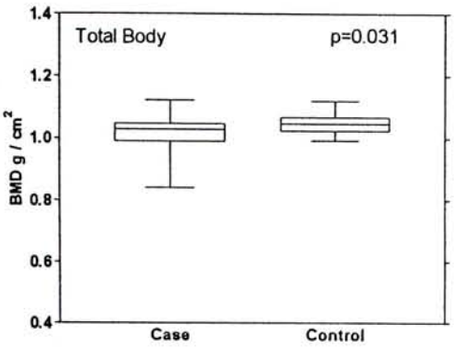
R^2=0.67, p=0.01

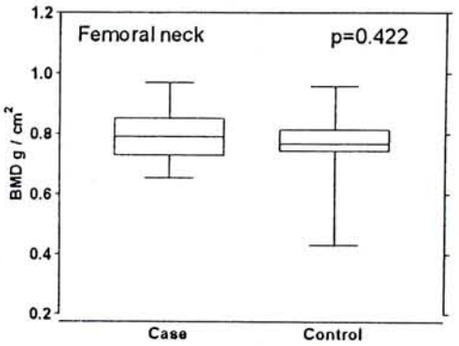
Table 6.4e. Multiple regression of Ward's triangle BMD against various variables in all OAD patients on inhaled steroids

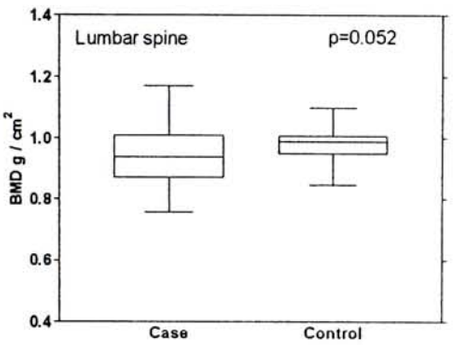
Independent variable	B	SE B	p-value
Age (year)	$-1.0e^{-02}$	$1.7e^{-03}$	0.00
Sex (male/female)	$-5.9e^{-02}$	$6.3e^{-02}$	0.36
Duration of Asthma (year)	$-1.7e^{-03}$	$1.6e^{-03}$	0.29
BMI (kg/M^2)	$7.8e^{-03}$	$7.3e^{-03}$	0.30
Daily dietary calcium intake (mg)	$-5.9e^{-05}$	$2.6e^{-04}$	0.83
Cumulative dose of oral steroids (mg)	$-7.7e^{-04}$	$4.5e^{-04}$	0.11
Cumulative dose of inhaled steroids (mg)	$1.2e^{-06}$	$2.1e^{-06}$	0.56
Current dose of inhaled steroids (μg per day)	$-1.1e^{-05}$	$7.7e^{-05}$	0.89
Length of inhaled steroids use (week)	$4.3e^{-04}$	$3.3e^{-03}$	0.90
Constant	1.0		

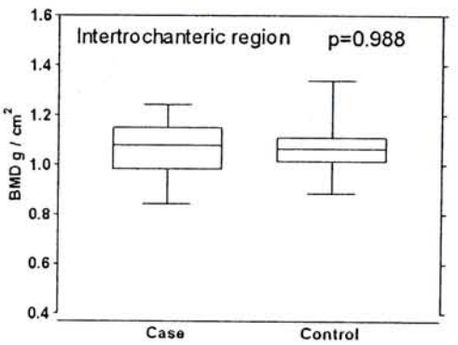
$R^2 = 0.76$, $p = 0.00$

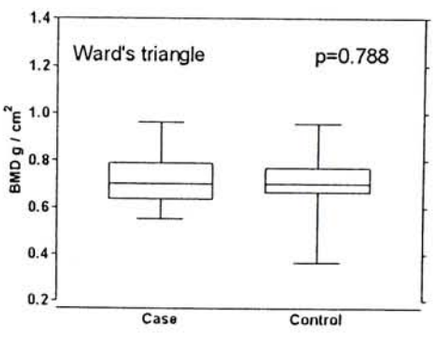
FIgure 6.1. Comparsion of BMDs (g /cm^2) in 37 premenopausal OAD patients on inhaled steroids and 74 age and BMI matched control subjects









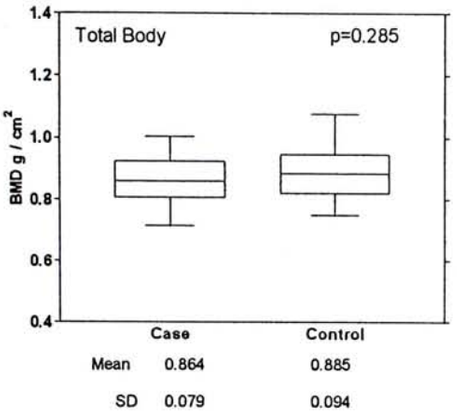


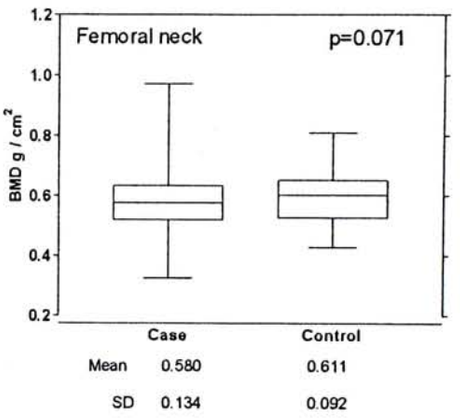
Box and whiskers

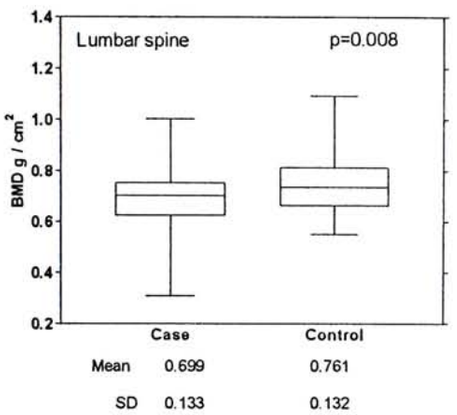
The box extends from 25th percentile to the 75th percentile, with a hortizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest.

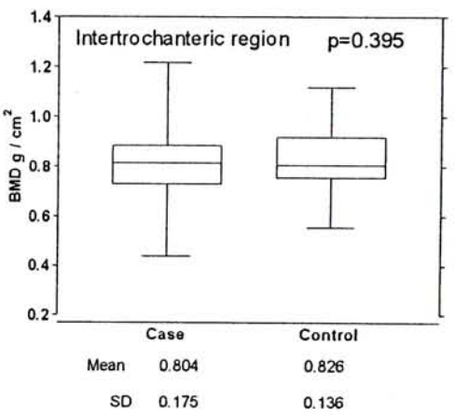
p-values are of paired t-tests, the paired t-tests preformed on the BMD value of OAD patient on inhaled steroids to the mean BMD values of two age and BMI matched normal subjects

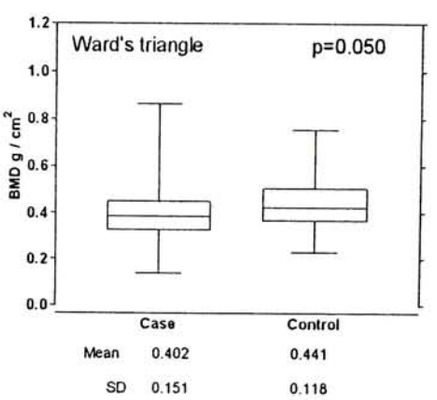
FIgure 6.2. Comparsion of BMDs (g /cm^2) in 36 postmenopausal OAD patients on inhaled steroids and 72 age and BMI matched control subjects









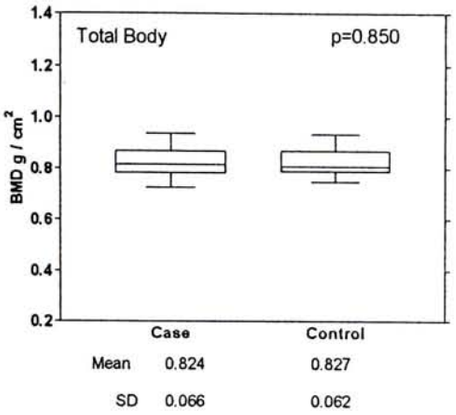


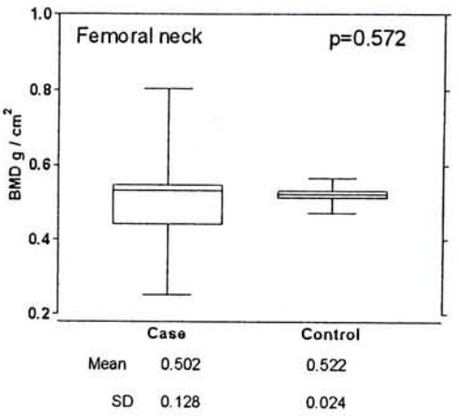
Box and whiskers

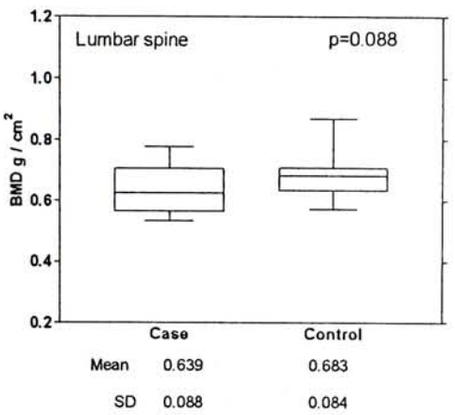
The box extends from 25th percentile to the 75th percentile, with a hortizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest.

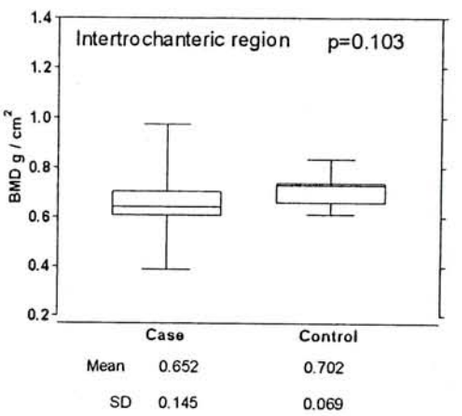
p-values are of paired t-tests, the paired t-tests preformed on the BMD of OAD patient on inhaled steroids to the mean BMD values of two age and BMI mateched normal subject

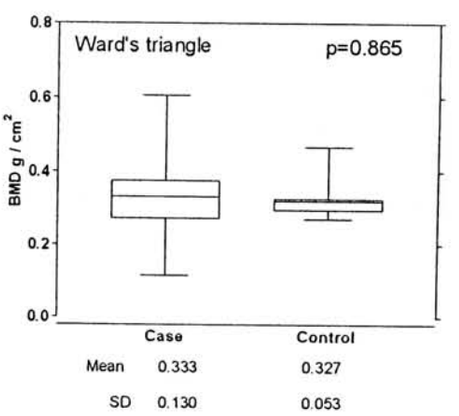
Figure 6.3. Comparsion of BMDs (g /cm^2) in 14 postmenopausal OAD patients not on inhaled steroids and 28 age and BMI matched control subjects









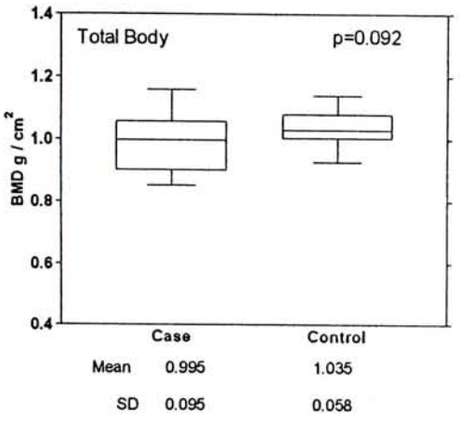


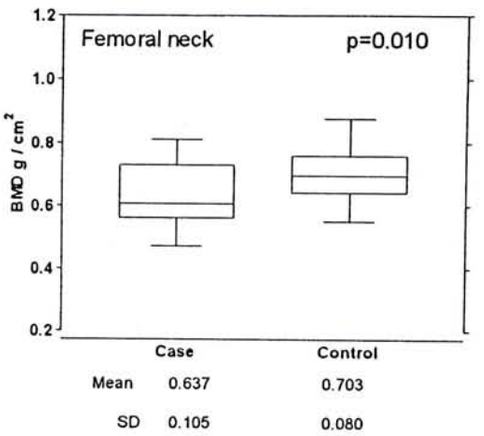
Box and whiskers

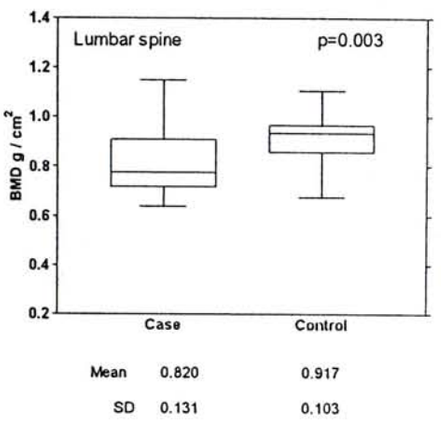
The box extends from 25th percentile to the 75th percentile, with a hortizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest.

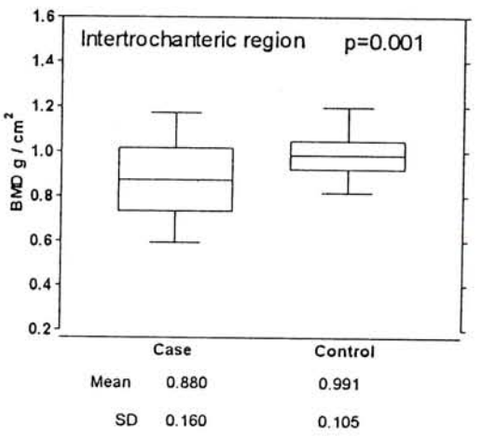
p-values are of paired t-tests, the paired t-tests preformed on the BMD value of OAD patient on inhaled steroids to the mean BMD values of two age and BMI mateched normal subjects

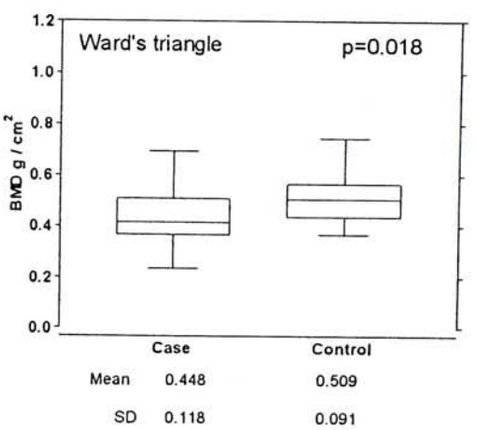
Figure 6.4. Comparsion of BMDs (g /cm^2) in 33 OAD male patients on inhaled steroids and 66 age and BMI matched control subjects









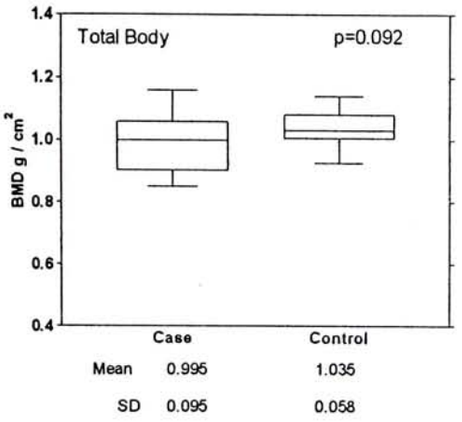


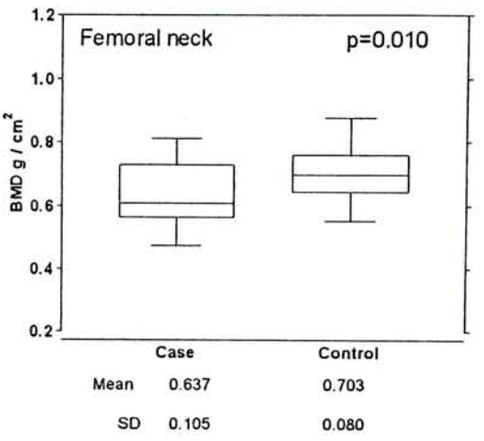
Box and whiskers

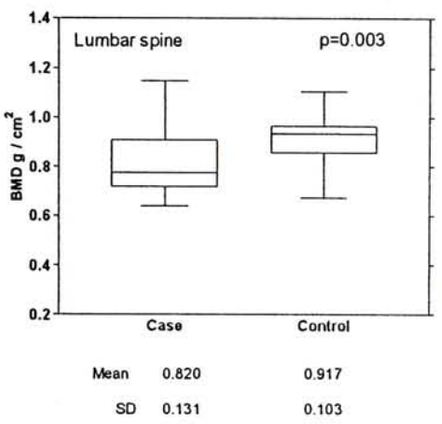
The box extends from 25th percentile to the 75th percentile, with a hortizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest.

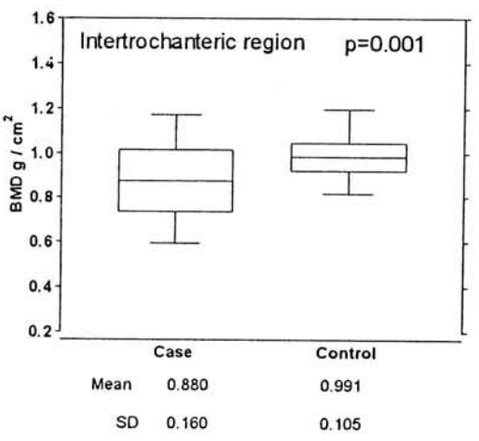
p-values are of paired t-tests, the paired t-tests preformed on the BMD value of OAD patient on inhaled steroids to the mean BMD values of two age and BMI mateched normal subjects

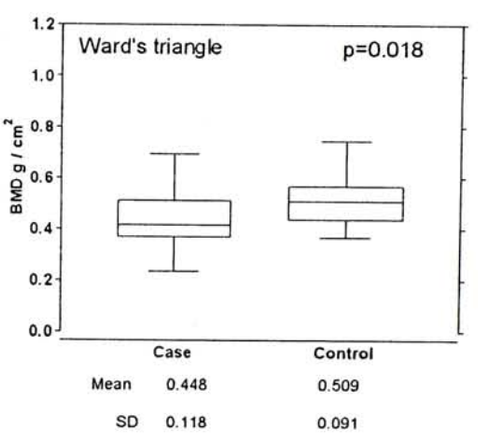
FIgure 6.5. Comparsion of BMDs (g /cm^2) in 24 OAD male patients not on inhaled steroids and 48 age and BMI matched control subjects









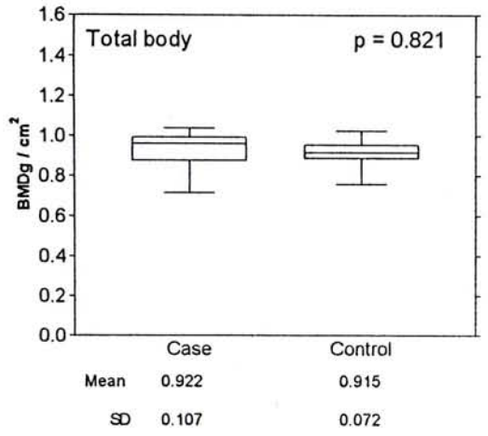


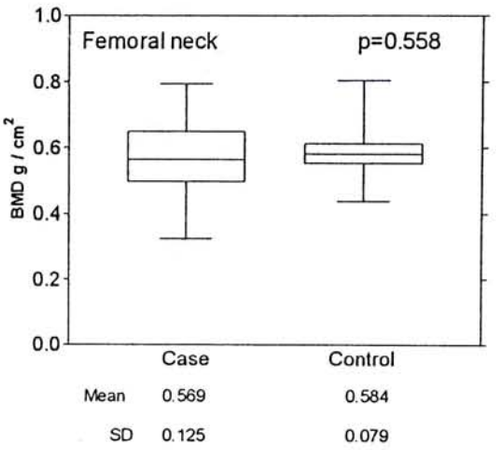
Box and whiskers

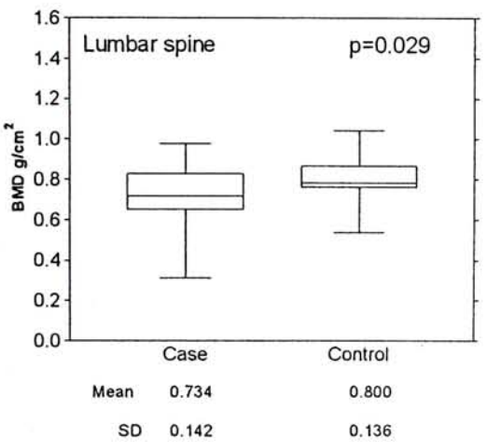
The box extends from 25th percentile to the 75th percentile, with a hortizontal line at the median (50th percentile). Whiskers extend down to the smallest value and up to the largest.

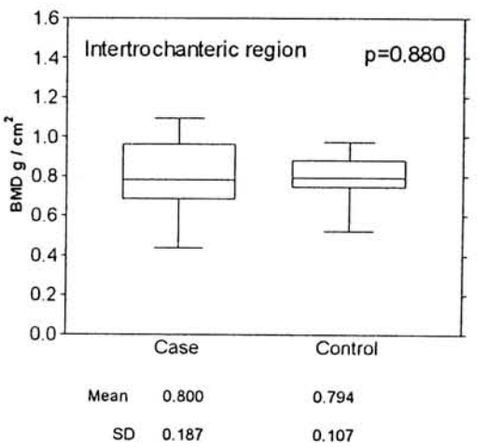
p-values are of paired t-tests, the paired t-tests preformed on the BMD value of OAD patient on inhaled steroids to the mean BMD values of two age and BMI mateched normal subjects

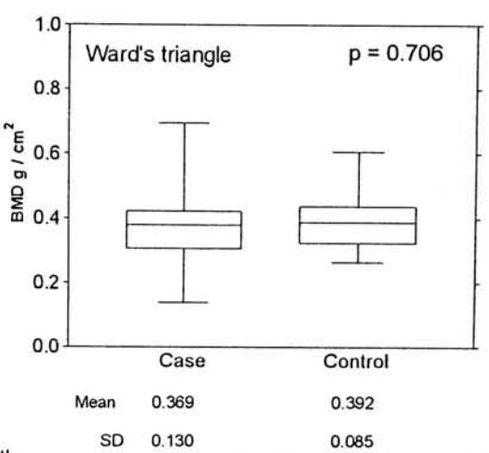
Figure 6.6. Comparsion of BMDs (g/cm^2) in 24 OAD patients on inhaled steroids and 24 OAD patient not on inhaled steroid











Box and whiskers.

The box extends from the 25thpercentile to the 75thpercentile, with a hortizontal line at the median (50th percentile).Whiskers extend down to the smallest value and up to the largest.

Paird t-tests

p-values are of paired t-tests, each OAD patient on inhaled steroids was matched with one OAD patient not on inhaled steroid for age, sex and BMI

Chapter 7 Results for phase II: Fluoride and Calcium trial

7.1. Factors affects the power of studies

The statistically power was reduced by the small sample size, the minimum required patients of 20 for each of the Tridin or the calcium groups in the permuted blocks of A, B and C were not met(Table 5.1). Thirty-seven, 36, and 33 OAD patients on inhaled steroid were recruited for blocks A, B and C, respectively. In addition, the power was further reduced as the OAD patients taking Tridin or calcium from each block were matched according to sex, age and BMI to minimum their confounding effects. These corresponding to 13, 13 and 15 OAD pairs of patients for each of the blocks A, B and C, respectively(Chart 7.1). Furthermore, only 8, 8 and 12 OAD pairs of patients completed the nine months clinical trial. The power of the study was further reduced to less than 0.5.

Effect of sample size on statistical power with statistical difference of 0.8, and type 1 error of 0.05 between the Tridin group and the calcium

Block								
A: Premenopausal			B: Postmenopausal			C: Men aged over 45		
n	d_r	Power	n	d_r	Power	n	d_r	Power
20	0.8	0.7	20	0.8	0.7	20	0.8	0.7
13	0.8	0.5	13	0.8	0.5	15	0.8	~0.6
8	0.8	<0.5	8	0.8	<0.5	12	0.8	0.5

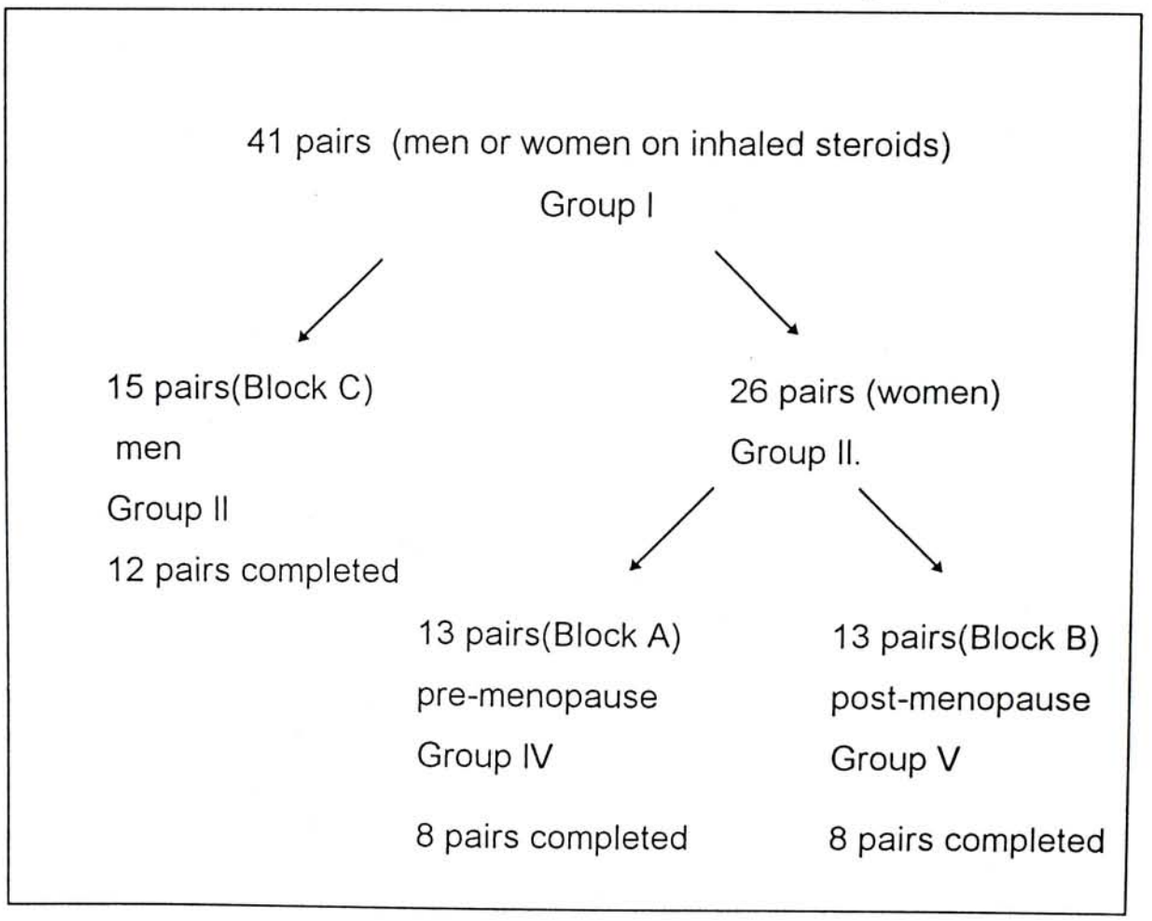
n: Sample size per group

dr = Magnitude of difference to be detected between the groups

7.2. Clinical findings

Forty-one pairs of OAD men and women on inhaled steroids matched with age, sex, menopausal status(for female) and BMI were included for the trial. They were stratified into: Group 1, consisted of all 41 matched pairs of OAD patients, group II consisted of 15 pairs of men patients; group III, consisted of 26 pairs of women patients; group IV, consisted of 13 pairs of pre-menopausal women and group V consisted of 13 pair post-menopausal patients (Chart 7.1.)

Chart 7.1 Stratification for the Tridin or the calcium group



The demographic and lifestyle factors of the age, sex and BMI match-paired patients at baseline were presented in tables 7.1a to 7.1e. There were no statistically significant differences in the above factors between the

match-paired patients by paired t-test. Both cumulative doses of oral, and inhaled steroids and loading bearing exercise were similar among all the paired groups. Also, other baseline characteristics such as daily dietary calcium intake, alcohol consumption and cigarette smoking habits were similar(Table 7.1 a.).

Sixty two patients completed the nine months clinical trial. Of these, thirty pairs of age sex and BMI matched pairs were included in the analysis. Two patients of the calcium group had to be excluded from for the analysis since their Tridin matched counterparts discontinued the trial. Of the 30 age, sex and BMI matched pairs, 12 were OAD men, 9 were OAD pre-menopausal women and 9 were OAD post-menopausal women.

Of the 20 patients discontinued the trial: 11 from the fluoride group and 9 from the calcium group. The reasons for discontinuing the trial were intolerable side effects in 6, personal reasons in 6, deaths not related to the trial in 3, being uncooperative in 4 and loss to follow up in 1(Table 7.5a). Thirty subjects completed the trial in the Tridin group (Drug intake compliance: 59 ± 24 %) whilst 32 patients completed the calcium trial (Drug intake compliance: 67 ± 24 %). There was no statistically significant difference in completeness of treatment between the two groups.

The Tridin treated group experienced about 1.9 times of the side effects as many as the group given calcium. The side effects fell into one of the two major categories, those due to gastric irritation and those due to pain in the lower extremities or both(table 7.5.b).

The gastric symptoms consisted mainly of nausea, or less commonly, epigastric pain and vomiting, or both. The Tridin treated group had the symptom 1.4 times as many as the patients taken calcium(table 7.5.b).

Lower extremity pain developed relatively acute associated with the start of treatment. The patients given Tridin had 1.8 times more episodes than those of the patients given calcium. The symptoms usually disappeared a few weeks after the treatments were stopped. Only three patients of the calcium group experienced muscle pain. Nineteen had no complaint about the side effect in the group given Tridin compared to 25 in the group given calcium(table 7.5b).

7.3. Body measurements and bone mineral densitometry

The means and SDs of the baseline bone densities for the forty-one age, sex, and BMI matched pairs patients were presented in tables 7.2a. There were statistically significant differences in percentage of body fat, lean body mass, and lumbar spine BMD between the fluoride and the calcium groups. However, with stratification based on sex, and menopausal status, the percentage of fat and lean body mass were no longer statistically significant(Table 7.2b-e). A scatter plot on the baseline lumbar spine BMD showed one person assigned to the calcium group had lower BMD(Figure 7.6). By stratification, it was revealed such patient belonged to the OAD female group(Table 7.2.c).

The means and SDs of the baseline characteristics for the thirty age, sex, and BMI matched pairs of OAD patients on inhaled steroids who have completed the Tridin or calcium treatments were presented in tables 7.3a to 7.3e. There were no statistically significant differences in any of the parameters listed.

The individual changes in BMDs at the lumbar spine and hip for each treatment groups were shown in figures 7.1 to 7.5. There was a wide scatter of percentage changes for the hip BMD(Figure 7.1). Subjects with extreme changes were not excluded from the analysis. The percentage changes in bone densities of the hip and spine were presented in table 7.4.a to 7.4.e. The BMDs of the hip and lumbar spine decreased in both groups of patients taking Tridin or calcium. However, the differences in these BMDs were not statistically significant by paired t-test.

The mean decrease in BMD of the lumbar spine was -11 ± 9 % in the Tridin group as compared to -9 ± 9 % in the calcium group(p value was not significant). The corresponding decrease in the bone mineral density of the femoral neck were -13 ± 9 % in the Tridin group as compared to -11 ± 9 % in the calcium group(p value not significant); for the intertrochanteric region -13 ± 8 % for the Tridin group and 12 ± 10 % for the calcium control; and for the Ward's triangle, -14 ± 11 % for the Tridin group compared to -10 ± 10 % for the calcium group(Table 7.4.a, and Figure 7.1a). Results for other groups were presented in table 7.4b to e, and figure 7.1 to 7.5.

Patients given Tridin or calcium showed bone losses in all the sites studied. The Tridin group showed a bigger fall in bone mineral densities than the group given calcium, but there were no significant differences between the two groups. The only site showing significant difference between the two groups was the Ward's triangle of the male OAD patients(Group II, $p<0.05$) (Table, 7,4b, Figure 7.3). Few patients taking either Tridin or calcium treatment showed increases in BMDs(Table 7.7).

Table 7.1a: Baseline characteristics of all the OAD patients on inhaled steroids at start of the clinical trial (mean ± SD)

n=	Tridin 41	Calcium 41
Age (year)	54 ± 17	55 ± 15
Age of menarche among female (year)	10 ± 8	9 ± 7
Age of menopause among female (year)	48 ± 5	50 ± 6
Oral steroid user (%)		
Never	73	73
ever	27	27
Cumulative dose of oral steroids (mg)	1295 ± 1237	411 ± 12
Duration of use of inhaled steroids (weeks)	40 ± 13	45 ± 13
Cumulative dose of inhaled steroids (mg)	389 ± 200	416 ± 160
Daily dietary calcium (mg)	213 ± 95	214 ±112
Alcohol drinking (%)		
never	93	76††
ever	7	24
Years of drinking among alcohol drinker	15 ± 6	27 ± 16
Alcohol intake among drinker (g/week)	182 ± 160	139 ± 136
Cigarette smoking(%)		
never	54	68
ever	46	32
Years of smoking among cigarette smoker	31 ± 13	31 ± 12
Cigarette pack year among smoker	25 ± 21	39 ± 25
Loading bearing exercise (hour/week)	0.1 ± 0	0.1 ± 0
Ever use oral contraceptives (OC) among women(%)		
yes	65	73
no	35	27
Months of OC use among women OC user	46 ± 71	12 ± 14

Paired T-test:

** $p < 0.01$

Chi-square test

†† $p<0.01$

Table 7.1b: Baseline characteristics of all OAD male patients on inhaled steroids at start of the clinical trial (mean ± SD)

n=	Tridin 15	Calcium 15
Age	63 ± 9	64 ± 9
Oral steroid user (%)		
Never	47	87[†††]
Ever	53	13
Cumulative dose of oral steroids (mg)	1295 ± 1237	411 ± 12
Duration of inhaled steroid (week)	36 ± 9	42 ± 11
Cumulative dose inhaled steroids (mg)	57 ± 23	53 ± 23
Daily dietary calcium (mg)	397 ± 160	373 ± 159
Alcohol drinking(%)		
never	80	47[†††]
ever	20	53
Years of drinking among alcohol drinker	15 ± 6	27 ± 13
Alcohol intake among alcohol drinker (g/week)	182 ± 160	125 ± 120
Cigarette smoking(%)		
never	20	20
ever	80	80
Years of smoking among cigarette smoker	33 ± 11	32 ± 12
Cigarette pack year among smoker	29 ± 17	42 ± 25
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0

Chi-square test
[†††] $p<0.001$

Table 7.1c: Baseline characteristics of all OAD female patients on inhaled steroids at start of the clinical trial (mean ± SD)

n=	Tridin 26	Calcium 26
Age	49 ± 18	49 ±16
Age of menarche	14 ± 2	15 ± 3
Age of menopause	48 ± 5	50 ± 6
Oral steroid user (%)		
Never	89	65†††
ever	11	35
Cumulative dose of oral steroids (mg)	0 ± 0	0 ± 0
Duration of use of inhaled steroids (week)	43 ± 15	47 ± 14
Cumulative dose of inhaled steroids (mg)	384 ± 223	441 ± 158
Daily dietary calcium (mg)	216 ± 95	229 ± 114
Alcohol drinking(%)		
never	100	92
ever	0	8
Years of drinking among alcohol drinker	0 ± 0	26 ± 34
Alcohol intake among alcohol drinker (g/week)	0 ± 0	195 ± 239
Cigarette smoking(%)		
never	73	96†††
ever	27	4
Years of smoking among cigarette smoker	27 ± 17	20 ± 0
Cigarette pack year among smoker	18 ± 26	10 ± 0
Loading bearing exercise (hour/week)	0.0 ± .0	0.1 ± 1
Ever use oral contraceptives (OC) (%)		
Never	65	73
Ever	35	27
Months of OC use among OC user	46 ± 71	12 ± 14

Chi-square test:

††† $p<0.05$

Table 7.1d Baseline characteristics of OAD premenopausal female patients on inhaled steroids at start of the clinical trial (mean ± SD)

n=	Tridin 13	Calcium 13
Age	33 ± 7	35 ± 8*
Age of menarche among female	14 ± 2	14 ± 2
Oral steroid user (%)		
Never	92	62†††
ever	8	38
Cumulative dose of oral steroids (mg)	0 ± 0	0 ± 0
Duration of use of inhaled steroids (weeks)	41 ± 18	49 ± 16
Cumulative dose of inhaled steroids (mg)	321 ± 234	460 ± 189
Daily dietary calcium (mg)	241 ± 77	211 ± 93
Alcohol drinking(%)		
never	100	100
ever	0	0
Years of drinking among alcohol drinker	0 ± 0	0 ± 0
Alcohol intake among alcohol drinker	0 ± 0	0 ± 0
Cigarette smoking(%)		
never	92	100
ever	8	0
Years of smoking among cigarette smoker	4 ± 0	0 ± 0
Cigarette pack year among smoker	1 ± 0	0 ± 0
Loading bearing exercise (hour/week)	0.0 ± 0	0.1 ± 0
Ever use oral contraceptives (OC)(%)		
never	39	54†
ever	61	46
Months of OC use among OC user	23 ± 18	12 ± 15

Paired t-test:

* $p < 0.05$

Chi-square test:

† $p<0.05$

††† $p<0.001$

Table 7.1e Baseline characteristics of OAD postmenopausal female patients on inhaled steroids at start of the clinical trial (mean ± SD)

	Tridin 13	Calcium 13
Age	66 ± 7	63 ± 6
Age of menarche	15 ± 2	17 ± 3*
Age of menopause	48 ± 5	50 ± 6
Oral steroid user (%)		
Never	85	69
ever	15	31
Cumulative dose of oral steroids (mg)	0 ± 0	0 ± 0
Duration of use of inhaled steroids (week)	45 ± 13	45 ± 13
Cumulative dose of inhaled steroids (mg)	447 ± 201	423 ± 124
Daily dietary calcium (mg)	191 ± 107	247 ± 133
Alcohol drinking(%)		
never	100	86ttt
ever	0	14
Years of drinking among alcohol drinker	0 ± 0	26 ± 34
Alcohol intake among alcohol drinker (g/week)	0 ± 0	195 ± 239
Cigarette smoking(%)		
never	54	92ttt
ever	46	8
Years of smoking among smoker	31 ± 14	20 ± 0
Cigarette pack year among cigarette smoker	21 ± 27	10 ± 0
Loading bearing exercise (hour/week)	0 ± 0	0.2 ± 1
Ever use oral contraceptives(OC) among female(%)		
never	92	92
ever	8	8
Months of OC use among OC user	228 ± 0	12 ± 0

Paired t-test:

* $p<0.05$

Chi-square test

ttt $p<0.001$

Table 7.2a: Baseline body measurement and bone mineral density of all OAD patients on inhaled steroids at baseline(mean ± SD)

	Treatment	
	Tridin	Calcium
n=	41	41
Body measurement		
Weight (kg)	58 ± 8	55 ± 14
Height (m)	1.6 ± 0	1.5 ± 0
BMI (kg/H^2)	24 ± 3	24 ± 4
Fat mass (kg)	20 ± 8	17 ± 15
% of body fat (kg)	36 ± 9	28 ± 18*
Lean body mass (kg)	36 ± 7	30 ± 18
Bone mineral density (gm/cm^2)		
Spine (L1-L4)	0.825 ± 0.181	0.654 ± 0.353**
Femoral neck	0.665 ± 0.143	0.668 ± 0.138
Intertrochanteric	0.904 ± 0.198	0.928 ± 0.169
Ward's triangle	0.519 ± 0.199	0.523 ± 0.192

Paired t-test

* $p < 0.05$

** $p < 0.01$

Table 7.2b Baseline body measurement and bone mineral density of OAD male patients on inhaled steroids at baseline(mean ± SD)

	Treatment	
	Tridin	Calcium
n=	15	15
Body measurement		
Weight (kg)	59 ± 7	57 ± 11
Height (m)	1.6 ± 0	1.6 ± 0
BMI (kg/H^2)	23 ± 3	22 ± 3
Fat mass (kg)	14 ± 5	9 ± 12
% of body fat (kg)	26 ± 5	19 ± 14
Lean body mass (kg)	41 ± 8	31 ± 25
Bone mineral density (gm/cm^2)		
Spine (L1-L4)	0.832 ± 0.157	0.726 ± 0.315
Femoral neck	0.644 ± 0.108	0.652 ± 0.102
Intertrochanteric	0.903 ± 0.162	0.894 ± 0.154
Ward's triangle	0.466 ± 0.112	0.458 ± 0.118

Table 7.2c: Baseline body measurement and bone mineral density of OAD female patients on inhaled steroids at baseline(mean ± SD)

	Treatment	
	Tridin	Calcium
n=	26	26
Body measurement		
Weight (kg)	57 ± 9	54 ± 16
Height (m)	1.5 ± 0	1.4 ± 0
BMI (kg/H^2)	25 ± 3	25 ± 5
Fat mass (kg)	24 ± 6	24 ± 15
% of body fat (kg)	41 ± 6	32 ± 19
Lean body mass (kg)	34 ± 4	29 ± 14
Bone mineral density (gm/cm^2)		
Spine (L1-L4)	0.822 ± 0.196	0.613 ± 0.373*
Femoral neck	0.673 ± 0.164	0.683 ± 0.153
Intertrochanteric	0.909 ± 0.222	0.943 ± 0.174
Ward's triangle	0.555 ± 0.212	0.557 ± 0.221

Paired t-tests
* $p < 0.05$

Table 7.2d: Baseline body measurement and bone mineral density of OAD pre-menopausal female patients on inhaled steroids at baseline(mean ± SD)

	Treatment	
	Tridin	Calcium
n=	13	13
Body measurement		
Weight (kg)	58 ± 9	53 ± 19
Height (m)	1.6 ± 0	1.4 ± 0
BMI (kg/H^2)	24 ± 3	24 ± 4
Fat mass (kg)	23 ± 6	24 ± 13
% of body fat (kg)	38 ± 5	34 ± 13
Lean body mass (kg)	35 ± 3	34 ± 5
Bone mineral density (gm/cm^2)		
Spine (L1-L4)	0.954 ± 0.127	0.701 ± 0.413
Femoral neck	0.791 ± 0.047	0.800 ± 0.106
Intertrochanteric	1.062 ± 0.101	1.069 ± 0.148
Ward's triangle	0.728 ± 0.099	0.746 ± 0.138

Table 7.2e: Baseline body measurement and bone mineral density of OAD post-menopausal female patients on inhaled steroids at baseline(mean ± SD)

	Treatment	
	Tridin	Calcium
n=	13	13
Body measurement		
Weight (kg)	56 ± 9	54 ± 12
Height (m)	1.5 ± 0	1.4 ± 0
BMI (kg/H^2)	25 ± 4	25 ± 5
Fat mass (kg)	25 ± 7	18 ± 17
% of body fat (kg)	43 ± 7	31 ± 24
Lean body mass (kg)	32 ± 3	24 ± 18
Bone mineral density (gm/cm^2)		
Spine (L1-L4)	0.689 ± 0.161	0.525 ± 0.319
Femoral neck	0.574 ± 0.144	0.546 ± 0.098
Intertrochanteric	0.824 ± 0.150	0.750 ± 0.161
Ward's triangle	0.385 ± 0.167	0.364 ± 0.098

Table 7.3 a: Baseline characteristics of the 30 pairs of OAD patients on inhaled steroids who have completed the Tridin and calcium clinical trial (mean ± SD)

n=	Tridin 30	Calcium 30
Age (year)	55 ± 16	54 ± 14
Age of menarche among female (year)	14 ± 2	15 ± 3
Age of menopause among female (year)	47 ± 5	51 ± 6
Oral steroid user (%)		
Never	73	73
ever	27	27
Cumulative dose of oral steroids (mg)	168 ± 328	146 ± 292
Duration of use of inhaled steroids (weeks)	40 ± 14	44 ± 11
Cumulative dose of inhaled steroids (mg)	394 ± 196	381 ± 120
Daily dietary calcium (mg)	216 ± 94	196 ± 81
Alcohol drinking (%)		
never	90	67
ever	10	33
Years of drinking among alcohol drinker	15 ± 6	27 ± 16
Alcohol intake among drinker (g/week)	91 ± 37	59 ± 46
Cigarette smoking(%)		
never	47	70
ever	56	30
Years of smoking among cigarette smoker	35 ± 8	34 ± 11
Cigarette pack year among smoker	36 ± 19	47 ± 21
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0
Ever use oral contraceptives (OC) among women(%)		
never	23	27
ever	67	73
Months of OC use among women OC user	1 ± 0	1 ± 0
Body measurement and bone mineral density (gm/cm^2)		
Weight (kg)	58 ± 8	57 ± 11
Height (m)	1.5 ± 0	1.5 ± 1
BMI (kg/H^2)	24 ± 3	24 ± 4
Fat mass (kg)	21 ± 6	20 ± 9
% of body fat (kg)	36 ± 8	34 ± 11
Lean body mass (kg)	37 ± 6	36 ± 8

Table 7.3 b: Baseline characteristics of the 12 pairs of OAD men on inhaled steroids who have completed the Tridin and calcium clinical trial (mean ± SD)

n=	Tridin 12	Calcium 12
Age (year)	62 ± 9	63 ± 8
Oral steroid user (%)		
Never	50	92
ever	50	8
Cumulative dose of oral steroids (mg)	239 ± 287	34 ± 116*
Duration of use of inhaled steroids (weeks)	35 ± 9	40 ± 12
Cumulative dose of inhaled steroids (mg)	354 ± 143	303 ± 72
Daily dietary calcium (mg)	216 ± 83	181 ± 109
Alcohol drinking (%)		
never	75	33
ever	25	67
Years of drinking among alcohol drinker	19 ± 1	30 ± 14
Alcohol intake among drinker (g/week)	91 ± 37	59 ± 46
Cigarette smoking(%)		
never	17	25
ever	83	75
Years of smoking among cigarette smoker	35 ± 8	34 ± 11
Cigarette pack year among smoker	36 ± 19	47 ± 21
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0
Body measurement and bone mineral density (gm/cm^2)		
Weight (kg)	56 ± 7	59 ± 11
Height (m)	1.6 ± 0	1.6 ± 0
BMI (kg/H^2)	23 ± 3	22 ± 3
Fat mass (kg)	16 ± 2	15 ± 5
% of body fat (kg)	27 ± 3	26 ± 4
Lean body mass (kg)	43 ± 5	44 ± 8

Paired t-test
* $p<0.05$

Table 7.3 c: Baseline characteristics of the 18 pairs of women OAD patients on inhaled steroids who have completed the clinical trial (mean ± SD)

n=	Tridin 18	Calcium 18
Age (year)	50 ± 18	48 ± 15
Age of menarche among female (year)	14 ± 2	15 ± 3
Age of menopause among female (year)	47 ± 5	51 ± 7
Oral steroid user (%)		
Never	89	11
ever	11	7
Cumulative dose of oral steroids (mg)	121 ± 353	222 ± 349
Duration of use of inhaled steroids (weeks)	43 ± 17	46 ± 10
Cumulative dose of inhaled steroids (mg)	422 ± 224	432 ± 119
Daily dietary calcium (mg)	216 ± 103	206 ± 56
Alcohol drinking (%)		
never	100	89
ever	0	11
Years of drinking among alcohol drinker	0 ± 0	26 ± 34
Alcohol intake among drinker (g/week)	0 ± 0	195 ± 239
Cigarette smoking(%)		
never	67	100†
ever	33	0
Years of smoking among cigarette smoker	0 ± 0	0 ± 0
Cigarette pack year among smoker	8 ± 8	0 ± 0
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0
Ever use oral contraceptives (OC) among women(%)	67	72
yes	33	28
no		
Months of OC use among women OC user	1 ± 0	1 ± 0
Body measurement and bone mineral density (gm/cm^2)		
Weight (kg)	57 ± 9	55 ± 10
Height (m)	1.5± 0	1.5± 0
BMI (kg/H^2)	25 ± 4	25 ± 5
Fat mass (kg)	23 ± 6	22 ± 9
% of body fat (kg)	41 ± 6	39 ± 10
Lean body mass (kg)	33 ± 4	32 ± 4

† Chi-square test $p<0.05$

Table 7.3 d: Baseline characteristics of the 9 pairs of pre-menopausal women OAD patients on inhaled steroids who have completed the clinical trial (mean ± SD)

n=	Tridin 9	Calcium 9
Age (year)	34 ± 6	36.8±9.4*
Age of menarche among female (year)	14 ± 2	13.0±1.4
Oral steroid user (%)		
Never	100	44†
ever	0	46
Cumulative dose of oral steroids (mg)	0 ± 0	350±432.9
Duration of use of inhaled steroids (weeks)	40 ± 19	44±11.4
Cumulative dose of inhaled steroids (mg)	322 ± 212	408±125.1
Daily dietary calcium (mg)	231 ± 77	214±69.5
Alcohol drinking (%)		
never	89	100
ever	11	0
Years of drinking among alcohol drinker	0 ± 0	0 ± 0
Alcohol intake among drinker (g/week)	0 ± 0	0 ± 0
Cigarette smoking(%)		
never	89	100
ever	11	0
Years of smoking among cigarette smoker	0 ± 0	0 ± 0
Cigarette pack year among smoker	0 ± 0	0 ± 0
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0
Ever use oral contraceptives (OC) among women(%)	67	33
never	33	67
ever		
Months of OC use among women OC user	0 ± 0	0 ± 0
Body measurement and bone mineral density (gm/cm^2)		
Weight (kg)	56 ± 10	55 ± 8
Height (m)	1.5 ± 0	1.5 ± 0
BMI (kg/H^2)	24 ± 3	24 ± 4
Fat mass (kg)	22 ± 6	20 ± 7
% of body fat (kg)	38 ± 5	38 ± 8
Lean body mass (kg)	35 ± 4	32 ± 4

Paired t-test:
* $p < 0.05$

Chi-square test
† $p < 0.05$

Table 7.3 e Baseline characteristics of the 9 pairs of post-menopausal women OAD patients on inhaled steroids who have completed the clinical trial (mean ± SD)

n=	Tridin 9	Calcium 9
Age (year)	67 ± 7	60 ± 9*
Age of menarche among female (year)	15 ± 2	17 ± 3
Age of menopause among female (year)	47 ± 5	515 ± 7
Oral steroid user (%)		
Never	78	78
ever	22	22
Cumulative dose of oral steroids (mg)	241 ± 481	93 ± 185
Duration of use of inhaled steroids (weeks)	47 ± 14	48 ± 10
Cumulative dose of inhaled steroids (mg)	521 ± 198	456 ± 114
Daily dietary calcium (mg)	201 ± 126	198 ± 40
Alcohol drinking (%)		
never	100	78
ever	0	22
Years of drinking among alcohol drinker	0 ± 0	0 ± 0
Alcohol intake among drinker (g/week)	0 ± 0	0 ± 0
Cigarette smoking(%)		
never	44	100†
ever	56	0
Years of smoking among cigarette smoker	0 ± 0	0 ± 0
Cigarette pack year among smoker	0 ± 0	0 ± 0
Loading bearing exercise (hour/week)	0 ± 0	0 ± 0
Ever use oral contraceptives (OC) among women(%)	100	78
yes	0	22
no		
Months of OC use among women OC user	0 ± 0	0 ± 0
Body measurement and bone mineral density (gm/cm^2)		
Weight (kg)	57 ± 9	56 ± 12
Height (m)	1.5 ± 0	1.5 ± 0
BMI (kg/H^2)	26 ± 4	25 ± 5.1
Fat mass (kg)	25 ± 6	24 ± 11
% of body fat (kg)	43 ± 6	40 ± 13
Lean body mass (kg)	31 ± 4	32 ± 3

Paired t-test:
* $p<0.05$

Chi-square test
† $p<0.05$

Table 7.4 a Bone mineral density of all OAD patients on inhaled steroids at baseline and at the end of the treatment and change in BMD (mean ± SD)

	Treatment					
	Tridin			Calcium		
n=	30			30		
	Before	After	% change in BMD	Before	After	% change in BMD
Bone mineral density (gm/cm^2)						
Spine (L1-L4)	0.823 ± 0.157	0.730 ± 0.128	-11 ± 9	0.804 ± 0.139	0.732 ± 0.133	-9 ± 9
Femoral neck	0.664 ± 0.128	0.580 ± 0.123	-13 ± 9	0.656 ± 0.108	0.600 ± 0.095	-11 ± 9
Intertrochanteric	0.939 ± 0.153	0.819 ± 0.147	-13 ± 8	0.902 ± 0.162	0.818 ± 0.143	-12 ± 10
Ward's triangle	0.510 ± 0.179	0.445 ± 0.166	-14 ± 11	0.504 ± 0.156	0.464 ± 0.129	-10 ± 10

Table 7.4 b Bone mineral density of the 12 male OAD patients on inhaled steroids at baseline and at the end of the treatment and change in BMD (mean ± SD)

	Treatment					
	Tridin			Calcium		
n=	12			12		
	Before	After	% change in BMD	Before	After	% change in BMD
Bone mineral density (gm/cm^2)						
Spine (L1-L4)	0.818 ± 0.151	0.720 ± 0.086	-11 ± 8.8	0.834 ± 0.123	0.765 ± 0.120	-8 ± 9.5
Femoral neck	0.635 ± 0.093	0.546 ± 0.086	-14 ± 8.7	0.653 ± 0.099	0.601 ± 0.092	-8 ± 8.4
Intertrochanteric	0.908 ± 0.146	0.782 ± 0.135	-14 ± 8.1	0.906 ± 0.155	0.827 ± 0.147	-9 ± 8.0
Ward's triangle	0.455 ± 0.112	0.378 ± 0.109	-17 ± 12.2	0.470 ± 0.126	0.435 ± 0.100	-6 ± 9.0*

Paired t-test between percentage change in BMD before and after Tridin and calcium treatment
* $p<0.05$

Table 7.4 c Bone mineral density of the 18 female OAD patients on inhaled steroids at baseline and at the end of the treatment and change in BMD (mean ± SD)

	Treatment					
	Tridin			Calcium		
n=	18			18		
	Before	After	% change in BMD	Before	After	% change in BMD
Bone mineral density (gm/cm^2)						
Spine (L1-L4)	0.827 ± 0.166	0.737 ± 0.152	-11 ± 8.6	0.785 ± 0.150	0.711 ± 0.140	-11 ± 9
Femoral neck	0.684 ± 0.147	0.603 ± 0.141	-13 ± 8.9	0.656 ± 0.116	0.599 ± 0.100	-13 ± 8
Intertrochanteric	0.959 ± 0.158	0.846 ± 0.153	-13 ± 8.1	0.899 ± 0.171	0.812 ± 0.144	-14 ± 11
Ward's triangle	0.547 ± 0.208	0.492 ± 0.145	-11 ± 8.8	0.526 ± 0.173	0.485 ± 0.145	-13 ± 11

Table 7.4 d Bone mineral density of the 9 pre-menopausal female OAD patients on inhaled steroids at baseline and at the end of the treatment and change in BMD (mean ± SD)

	Treatment					
	Tridin			Calcium		
n=	9			9		
	Before	After	% change in BMD	Before	After	% change in BMD
Bone mineral density (gm/cm^2)						
Spine (L1-L4)	0.954 ± 0.117	0.846 ± 0.098	-11 ± 9	0.887 ± 0.092	0.785 ± 0.112	-15 ± 8
Femoral neck	0.789 ± 0.047	0.683 ± 0.085	-13 ± 9	0.728 ± 0.066	0.643 ± 0.096	-16 ± 7
Intertrochanteric	1.078 ± 0.101	0.930 ± 0.109	-13 ± 8	0.990 ± 0.121	0.844 ± 0.168	-18 ± 13
Ward's triangle	0.714 ± 0.095	0.619 ± 0.101	-11 ± 9	0.660 ± 0.106	0.583 ± 0.109	-17 ± 8

Table 7.4 e Bone mineral density of the 9 post-menopausal female OAD patients on inhaled steroids at baseline and at the end of the treatment and change in BMD (mean ± SD)

	Treatment					
	Tridin			Calcium		
n=	9			9		
	Before	After	% change in BMD	Before	After	% change in BMD
Bone mineral density (gm/cm^2)						
Spine (L1-L4)	0.699±0.090	0.628±0.112	-10 ± 9	0.683±0.125	0.636±0.129	-7 ± 8
Femoral neck	0.579±0.137	0.514±0.140	-12 ± 8	0.584±0.112	0.550±0.084	-9 ± 9
Intertrochanteric	0.840±0.106	0.751±0.143	-11 ± 9	0.808±0.171	0.775±0.111	-9 ± 7
Ward's triangle	0.379±0.140	0.349±0.151	-9 ± 9	0.392±0.110	0.374±0.090	-9 ± 12

Table 7.5.a. Reasons for withdrawn from the Tridin and calcium clinical trial in the 20 OAD patients on inhaled steroids

Symptom / Number of patient	No. of patients		No. of episodes	
	Tridin	Calcium	Tridin	Calcium
GI discomfort	4	1	8	3
(Gastric pain, nausea, vomiting)				
Muscle pain	0	1	0	2
Died	1	2	NA	NA
No complaints	4	2	NA	NA
Others				
Lost to follow up	1	0		
Uncooperative	1	3		
Total number of withdrawn	11	9		
Number of patients completed the trial	30#	32		
Total number of patients	41	41		

Note: # Analysis were carried out based on these 30 pairs of patients, 2 patients from the calcium group was not used in the analysis since their corresponding Tridin match withdrawn from the trial

Table 7.5.b. Symptoms and side-effects from the Tridin and calcium clinical trial in the OAD patients on inhaled steroids

Symptom	No. of patients		No. of episodes	
	Tridin	Calcium	Tridin	Calcium
GI discomfort(%)				
(Gastric pain, nausea, vomiting)	13(32)	6(15)	25(76)	14(58)
Lower back pain(%)	6(15)	2(5)	8(24)	5(21)
Muscle pain(%)	0(0)	3(7)	0()	5(21)
Others(%)	2(5)	3(7)	NA	NA
Died	1(2)	2(5)	NA	NA
No complaints(%)	19(46)	25(61)	NA	NA
Total	41(100)	41(100)	33(100)	24(100)

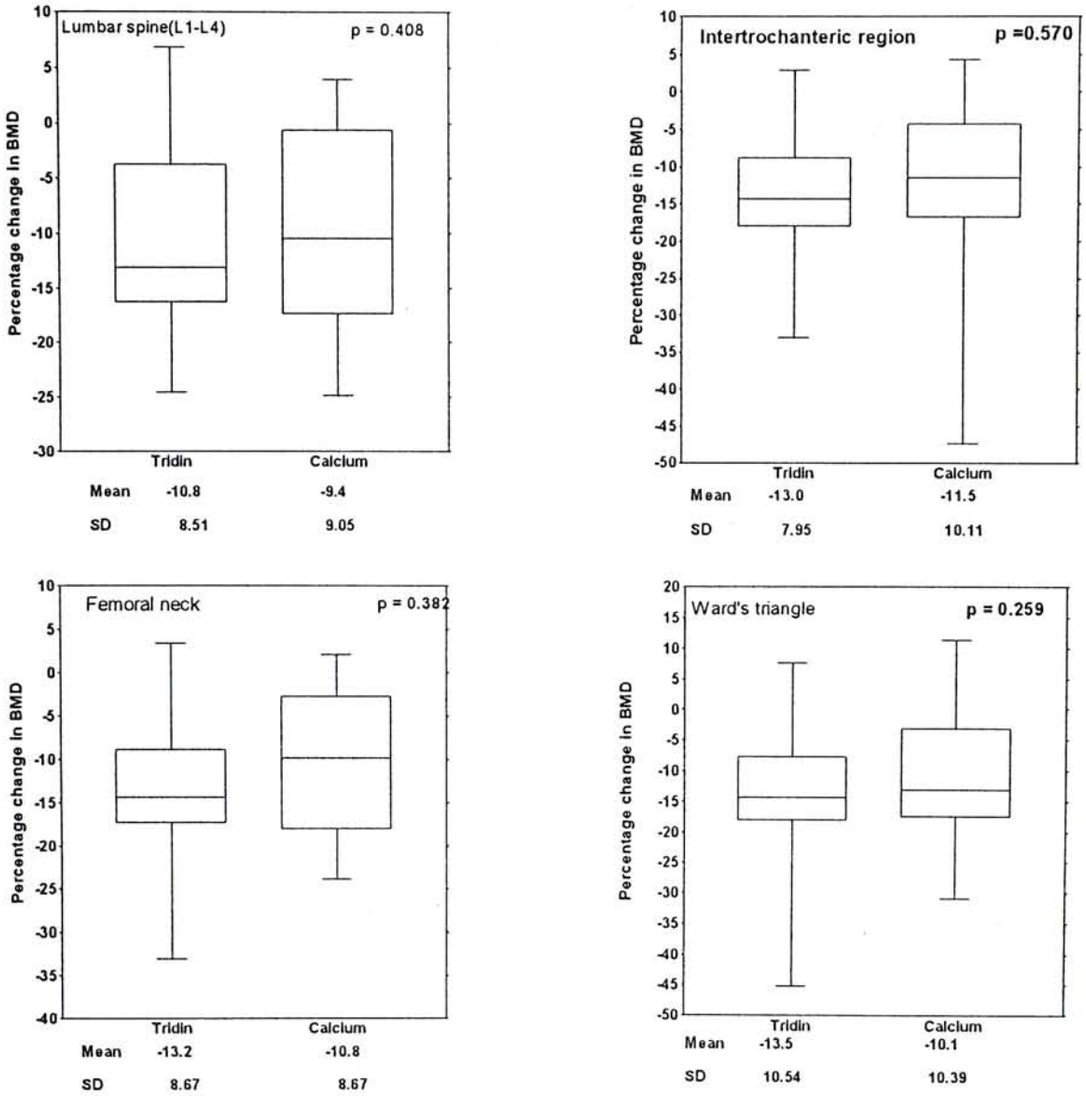
Table 7.6 Number of patients showing increase in BMD after treatment

Number of patients(%)	Group I All patients (*n*=30)	Group II Male (*n*=12)	Group III Female (*n*=18)	Group IV Pre-menopausal (*n*=9)	Group V Post-menopausal (*n*=9)
Lumbar spine(L1-L4)					
Fluoride	3(10)	1(8)	2(11)	2(22)	0(0)
Calcium	8(27)	4(33)	4(22)	1(11)	3(33)
Femoral neck					
Fluoride	2(7)	1(8)	1(6)	1(11)	0(0)
Calcium	3(10)	2(17)	1(6)	0(0)	1(11)
Intertrochanteric region					
Fluoride	2(7)	0(0)	2(11)	1(11)	1(11)
Calcium	1(3)	1(8)	0(0)	0(0)	0(0)
Ward's triangle					
Fluoride	2(7)	0(0)	2(11)	0(0)	2(22)
Calcium	5(17)	4(33)	1(6)	0(0)	1(11)

Table 7.7 Compliance of Tridin or calcium intake for OAD patients on inhaled steroid completed the nine months clinical trial

Group	Tridin Mean ± SD(range)	Calcium Mean ± SD(range)
1:All patients(30)	59 ± 24 (16-100)	67 ± 24 (16-97)
2:Male patients(12)	56 ± 25 (16-100)	63 ± 24 (21-97)
3:Female patients(18)	63 ± 24 (20-94)	74 ± 24 (16-96)
4:Premenopausal female(9)	56 ± 27 (16-99)	60 ± 22 (28-93)
5:Postmenopausal female(9)	56 ± 24 (29-100)	65 ± 27 (21-97)

Figure 7.1. Effects of Tridin and Calcium supplementation on percentage changes on BMDs in 30 age and sex matched-pair of OAD Chinese patients



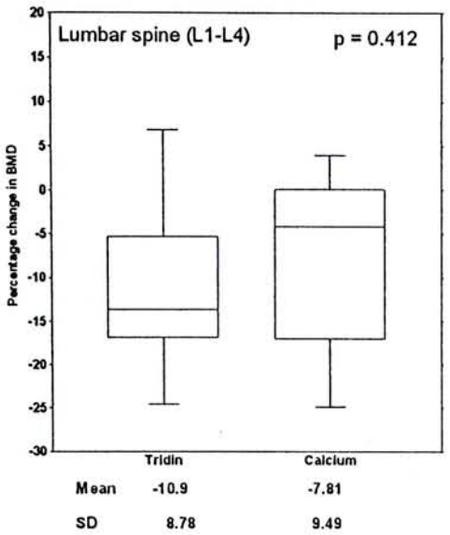
Box and whiskers

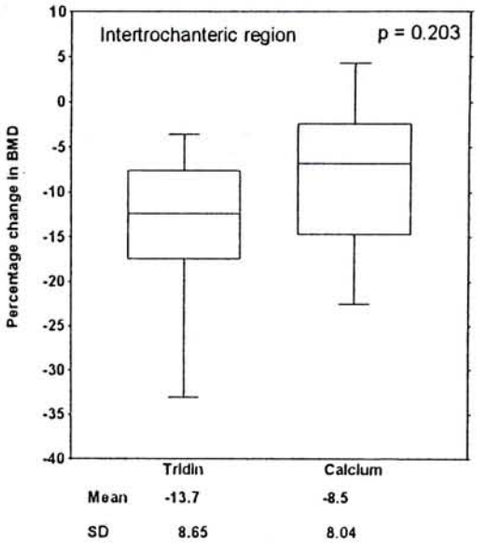
The box extends from the 25th percentile to the 75th percentile, with a hortizontal line at the median(50th percentile). Whiskers extend down to the smallest value and up to the largest.

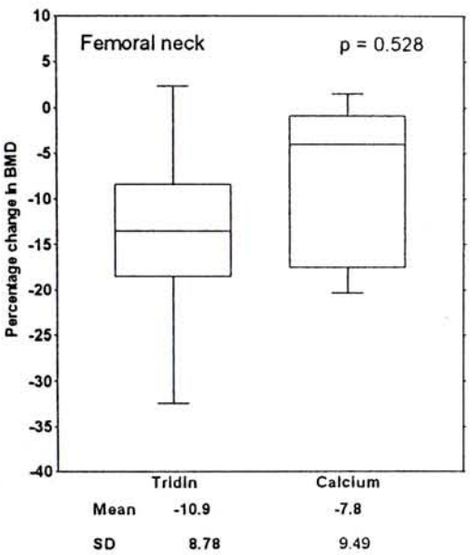
Paried t-tests

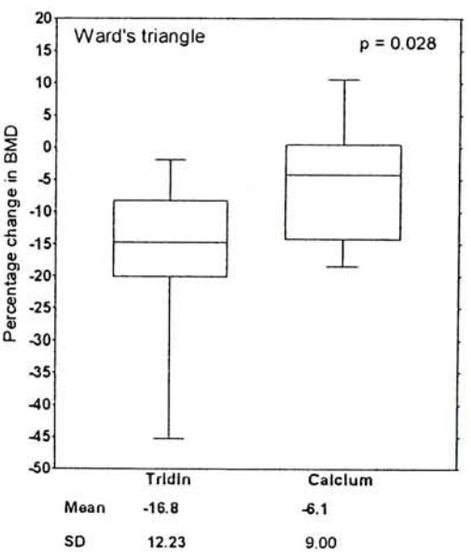
p-values are of paired t-test, OAD patient on inhaled steroids treated with tridine or calcium are matched for age, sex and BMI

Figure 7.2. Effects of Tridin and Calcium supplementation on percentage change on BMDs in 12 age and sex matched-pair of OAD male Chinese patients









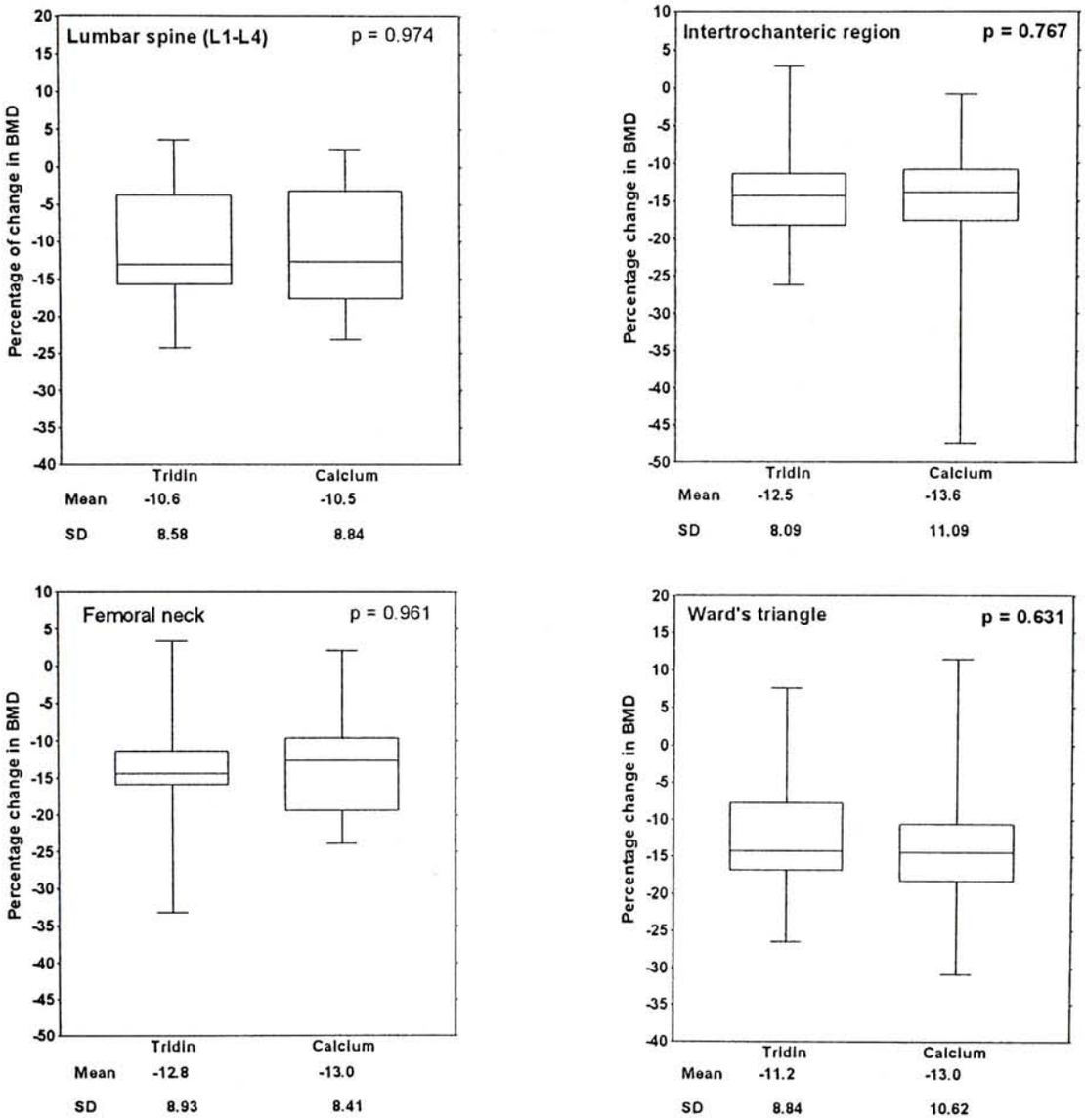
Box and whiskers

The box extends from the 25th percentile to the 75th percentile, with a hortizontal line at the median(50th percentile). Whiskers extend down to the smallest value and up to the largest.

Paried t-tests

p-values are of paired t-test, OAD patient on inhaled steroids treated with tridine or calcium are matched for age, and BMI

Figure 7.3. Effects of Tridin and Calcium supplementation on percentage changes on BMDs in 18 age and sex matched-pair of OAD female Chinese patients



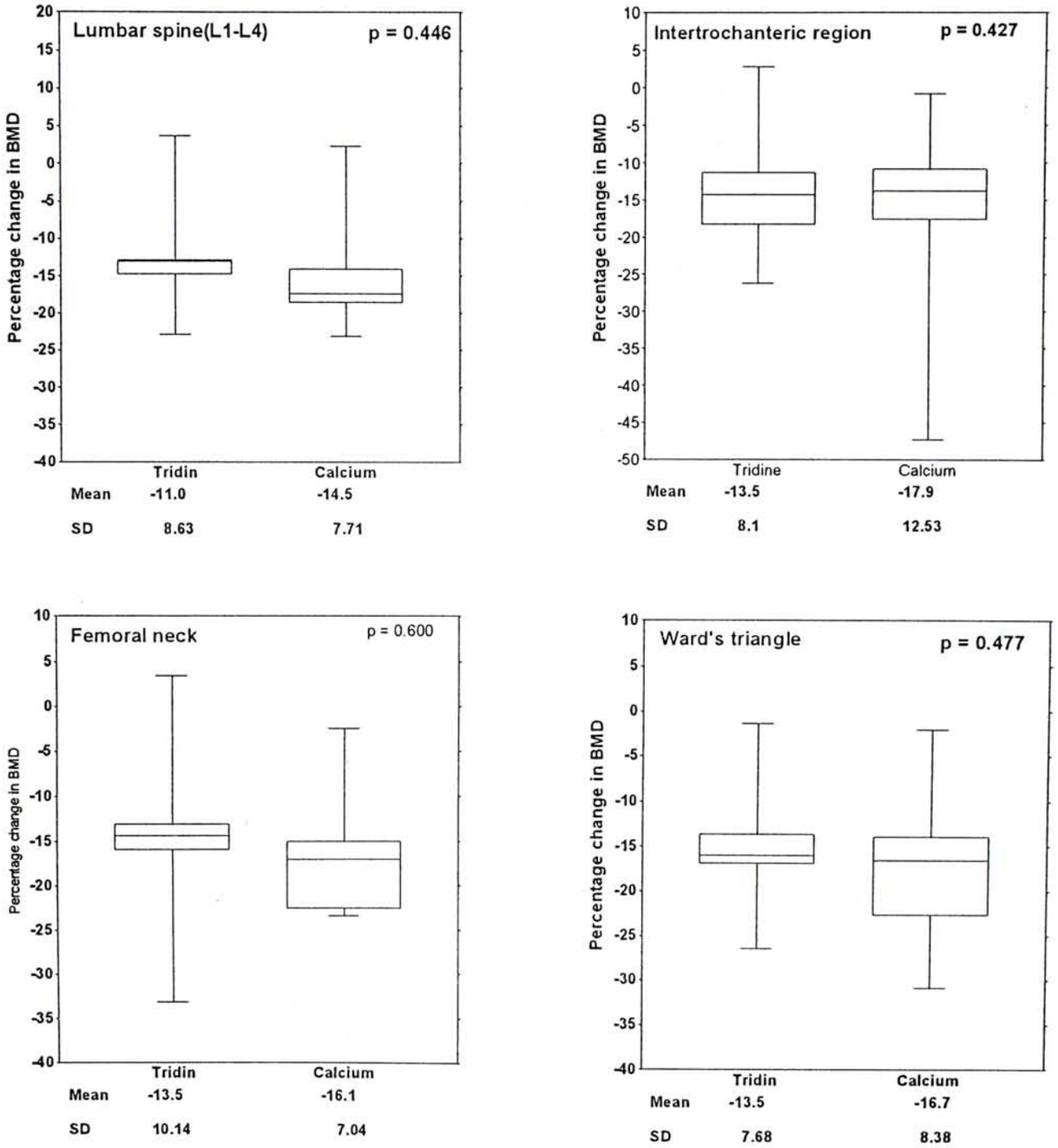
Box and whiskers

The box extends from the 25th percentile to the 75th percentile, with a hortizontal line at the median(50th percentile). Whiskers extend down to the smallest value and up to the largest.

Paried t-tests

p-values are of paired t-test, OAD patient on inhaled steroids treated with tridine or calcium are matched for age, and BMI

Figure 7.4. Effects of Tridin and Calcium supplementation on percentage change on BMDs in 9 age and sex matched-pair of OAD pre-menopasual female Chinese patients



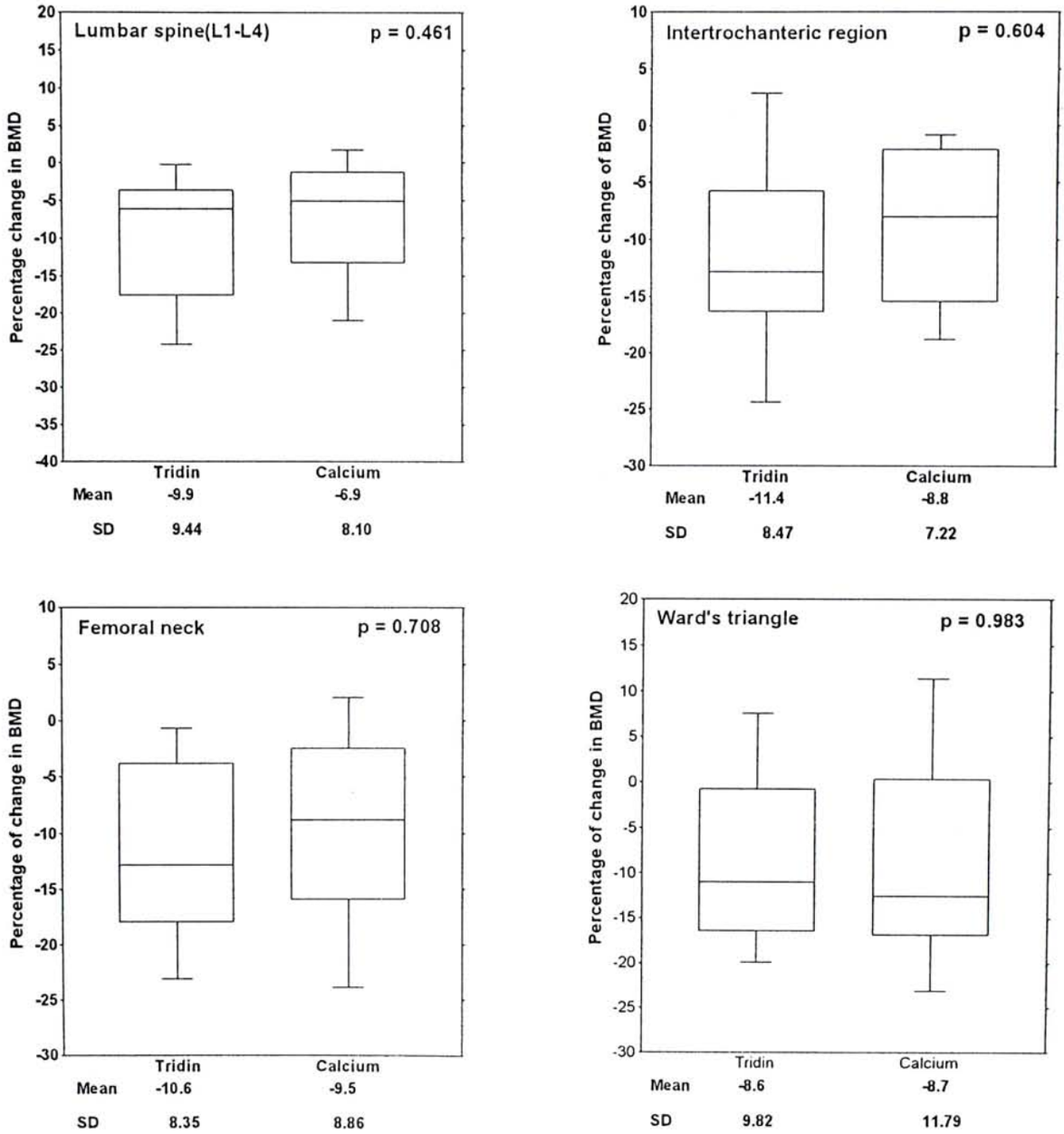
Box and whiskers

The box extends from the 25th percentile to the 75th percentile, with a hortizontal line at the median(50th percentile). Whiskers extend down to the smallest value and up to the largest.

Paried t-tests

p-values are of paired t-test, OAD patient on inhaled steroids treated with tridine or calcium are matched for age, and BMI

Figure 7.5. Effects of Tridin and Calcium supplementation on percentage change on BMDs in 9 age and sex matched pairs of OAD pre-menopausal female Chinese patient



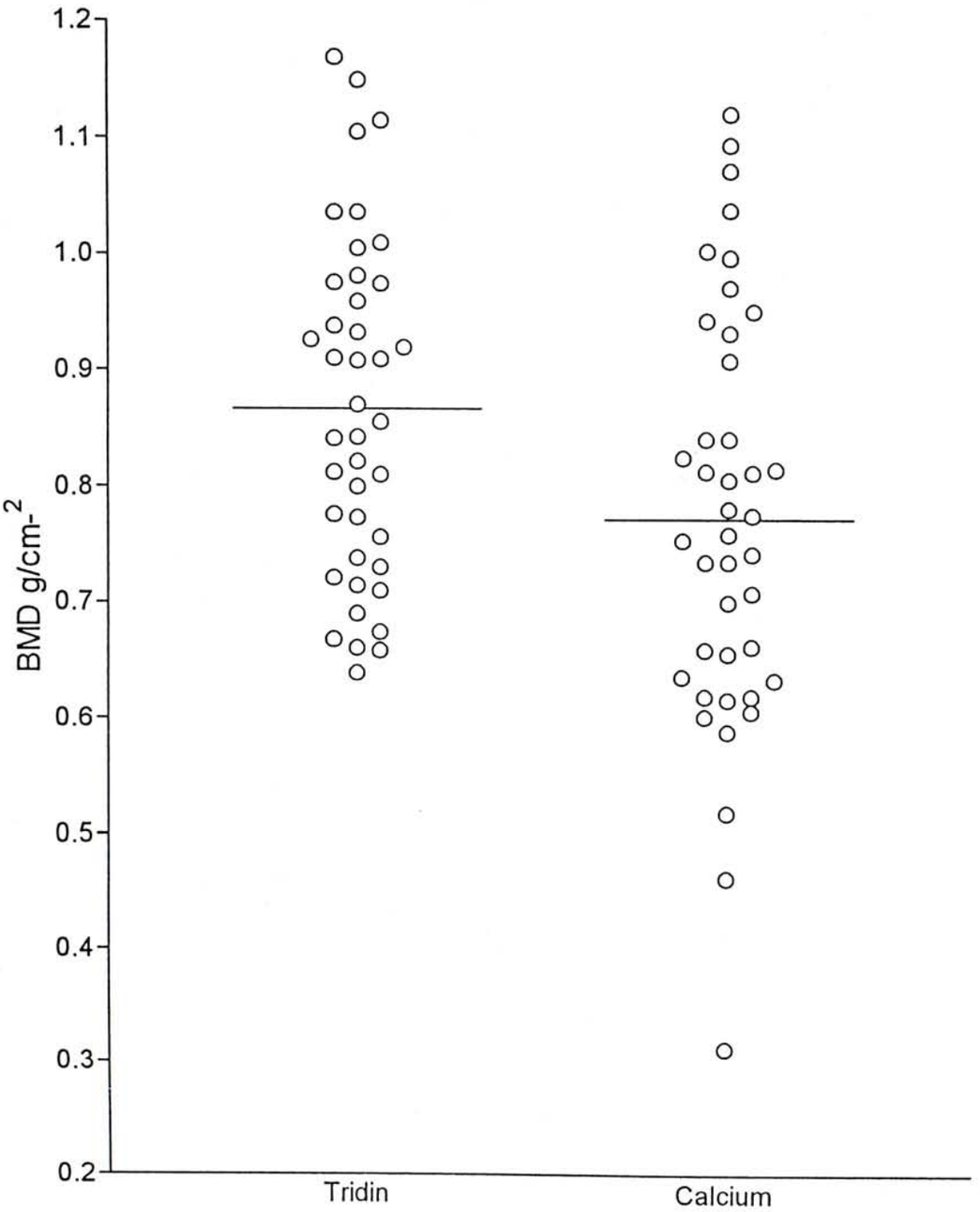
Box and whiskers

The box extends from the 25th percentile to the 75th percentile, with a hortizontal line at the median(50th percentile). Whiskers extend down to the smallest value and up to the largest.

Paried t-tests

p-values are of paired t-test, OAD patient on inhaled steroids treated with tridine or calcium are matched for age, and BMI

Figure 7.6. Baseline lumbar spine (L1-L4) BMD in 41 age and sex matched-pair of OAD Chinese patients on Tridin or calcium treatment



Chapter 8: Discussion for phase I

Inhaled steroids are clearly effective in improving the control of asthma and lung functions among OAD patients. They are considered as an established and safe mode of therapy(Tarlo, S. M., Broder, I. et al, 1988). It is generally believe that the impact of inhaled steroids on BMD is significantly less than that of therapeutically equivalent doses of oral steroids. Recently, the possible long term side effects of inhaled steroids therapy on bone densities of asthmatic or OAD patients have been studied, but no clear "dose and time threshold" have been established(Barnes, N. C., 1993).

Long-term systemic steroid therapy in OAD patients is associated with decreased trabecular bone density, and osteoporosis has been found to occur in 10-40% of OAD patients(Ruegsegger, P., Medici, T. C. et al, 1983; William, S. J., 1988).

Examination of biochemical indices suggests that inhaled corticosteroids may diminish bone formation as evidenced by a decrease in serum osteocalcin level(Teelucksingh, S., Padfield, P. L., et al, 1991), and an increase in bone resorption as shown by increased hydroxyproline output in urine(Ali, N. J., Capewell, S. et al, 1991). Conflicting results are reported on the study of the adverse effect on bone density. Some authors(Reid, D. M., Nicoll, J. J. et al, 1986) reported that the use of inhaled steroids in adults may also play a role in the development of osteoporosis, although recent data did not confirm this possibility(Baraldi, E., Bollini, M. C., et al, 1994).

Baraldi showed that therapy with inhaled beclomethasone diproprionate(BDP) (300 - 400 μg day^{-1}) does not cause bone density loss in asthmatic children treated over a period of six months.

Some of the problems associated with the BMD assessment include different methods and skeletal sites used, small number of patients included in the study, and the use of sub-optimally matched control subjects for comparison. In this study, normal healthy control subjects are carefully matched for factors known to potentially affect BMD such as age, sex, and BMI(Appendix 3). However, it is practically impossible to find patients with similar degree and duration of asthma who have not been treated with some steroid medications.

The BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Ward's triangle for the OAD premenopausal women on inhaled steroids, the OAD postmenopausal women on inhaled steroids, the OAD postmenopausal women not on inhaled steroids, the OAD men on inhaled steroids, and the OAD men not on inhaled steroids were analysed separately. The BMDs of the OAD men and women on inhaled steroids were compared with the OAD men and women not on inhaled steroids.

The results of this study suggest that therapy with inhaled steroid of 500 - 4000 μg day^{-1}, (n = 106) over a treatment period of 14 - 76 weeks did not greatly affect bone mineral density in women. Both the premenopausal and postmenopausal OAD women shown little changes in BMDs at the femoral neck(p value not significant), intertrochanteric region(p value not

significant) and Ward's triangle(p value not significant), except the lumbar spine($p<0.05$). These findings were similar to previously reported(Herrala, J., Puolijoki, H., et al, 1994) using 1000 μg / day for over 1 year.

The BMDs of lumbar spine($p<0.01$), femoral neck($p<0.05$), intertrochanteric region($p<0.01$) and Ward's triangle($p<0.05$) of male OAD patients on inhaled steroid were statistically significant lower than those of their matched normal controls. However, the disease itself could contribute to the loss of BMDs in these patients, since the male OAD patients not on steroid inhalers also had lower BMDs at these bone sites compared with their age matched normal controls. Furthermore, in these two groups of patients, the duration and quality of alcohol intake and cigarette smoking are greater. When the BMDs were adjusted for covarience, no statistically significant differences were found between the OAD men on inhaled steroids and their matched normal controls(table 6.3d). However, the BMDs of the femoral neck(Sig of $F=0.017$), intertrochanteric region(Sig of $F=0.003$) and Ward's triangle(Sig of $F=0.007$) of OAD men not on inhaled steroids were statistically significantly lower than those of their matched normal controls(table 6.3e). Moreover, only the BMD of the lumbar spine of the older OAD men and women on inhaled steroids was statistically significantly lower than that of the OAD men and women not on inhaled steroids(table 6.2f, table 6.3f.). These results suggest that inhaled steroids dose of 1374 ± 445 μg for 40 ± 11 weeks did not affect BMDs of the total body, lumbar spine, femoral neck, intertrochanteric region and Wards' triangle of OAD men.

The BMD of lumbar spine was significantly lower in the older OAD patients on inhaled steroids(table 6.3f), while the other bone sites were not affected by inhaled steroids.

The total body BMD results from all the OAD men and women groups on or not on inhaled steroids suggested that this is not affected by factors of using inhaled steroids, ageing, sex, cigarette smoking and alcohol consumption. These factors are more important in the loss of BMDs at the lumbar spine and the hip. Pre-menopausal women patients were least affected by inhaled steroids, and this is followed by the post-menopausal women, and the OAD men.

Factors which affect BMD include age, sex, BMI, fat mass, alcohol consumption and cigarette smoking. These factors may confound the relationships among OAD, steroid treatment and BMD.

Inhaled steroids ranging from 600-2000 μg per day for 14 to 64 weeks do not affect the total body and hip BMDs in the post-menopausal OAD women patients, but inhaled steroids ranging from 800-2250 μg per day for 20 to 62 weeks affects the spine and hip BMDs in OAD men patients($p < 0.05$ to $p < 0.001$). The BMD of lumbar spine of the OAD patients on inhaled steroids was significantly lower than that of the OAD patients not on inhaled steroids. The BMDs of total body, femoral neck, intertrochanteric region and Ward's triangle were lower than those of the OAD patients not on inhaled steroids but the differences were not significant.

These results suggest OAD men with smoking habits are more likely to be affected by inhaled steroids on their BMDs. The OAD women were less

affected. This might be explained by the fact that the pre-menopausal females do not reach peak bone mass until around 40 years of age. In this study the average age was of the pre-menopausal women was 36(Table 6.1), and the normal osteogenesis process might protect them from bone loss due to inhaled steroids therapy. In the postmenopausal group, the average age was 64 years old, and the mean body fat content was 31 %. High body fat may contribute towards higher BMD since the androstenedione in fat tissue is the principal source of oestrogen in postmenopausal women(Crilly, R. G., Cawood, M., et al, 1988).

Assessments of total dietary calcium by the frequencies recall method has several limitations, such as it is subject to recall bias, and food portion size variations. Several items should be added to the list, such as beef, pork and chicken, since they are frequently found in Chinese diet. Furthermore, food that has been taken frequently by the patient but not mentioned in the item list should be taken into account, and the calcium contents in such food item can be deduced from the food composition table assembled by the Royal Society of Chemistry, London(Royal Society of Chemistry, 1991).

Our findings differ from one of the previously reported Hong Kong study(Ip, M., Lam, K., et al, 1994). Ip and her colleagues found a significant decrease in BMDs of lumbar spine(L2-L4), femoral neck, trochanter, and Ward's triangle in 18 premenopausal women with mean age less than 41.5 years old using inhaled steroids, beclomethasone or budesonide, in average dose of 1,100 ± 510 μg / day for 40 ± 43.1 months(table 8.1). The difference between the two studies among premenopausal female OAD patients from

the same region and using similar selection criteria is unexpected. This is most likely due to the differences in the duration and cumulative dose of inhaled steroids among the patients since duration was longer and the dosage was higher among Ip's subjects compared with our patients. In addition, they found no statistical difference in the BMDs between men patients and their matched controls, in contrast to the finding of this study. The differences in the BMD between the men OAD patient and control groups of the two studies may be due to the differences in age between the two cohorts and in part due to the small sample size in Ip and her colleagues' study.

Table 8.1. Comparisons of demographic data between Ip and our premenopausal OAD patients on inhaled steroids

	(Ip, M. 1994)	Our premenopausal OAD female patients
Male : female ratio no	12:18	37 female
Age, year	33±10.0	36±7.4
BMI	21±3.2	25±3.6
Duration of use of inhaled steroid, (month)	40±43.1	10±3.8
Cumulative dose per patient, (mg)	932±1,023	389±179.5
Average daily dose, (μg)	1,100±510	1,310±569.1
Dietary calcium intake (mg per day)	536	216

CHAPTER 9: Discussion for phase II: Tridin and Calcium trial

Many previous studies have indicated that elemental fluoride can improve bone density. However there were conflicting reports on the type and quality of bone in subjects undergoing such treatment.

In this study, attempt has been made to evaluate the effect of elemental fluoride as monofluorophosphate on bone mineral density in OAD patients taking inhaled steroids. Age, sex and BMI matched OAD patients were either given monofluorophosphate - calcium tablets(Tridin) or calcium tablets without monofluorophosphate for nine months. At the end of the trial percentage changes in BMD were compared between the two groups by paired t-test.

Our results indicated that BMD decreased in both the Tridin and calcium treatment groups. The group treated by Tridin has a larger decrease in BMDs of the lumbar spine and three hip sites than the group given calcium only(table 7.4). However, there differences were not statistically significant. This was partly due to the small study sample size.

For the lumbar spine BMD, our results from both the Tridin or calcium groups were lower than that of Pouilles(Pouilles, J. M., Tremollieres, F., et al, 1991). For instance, in our all patients group (group I, table 7.4) showed an 8.6% decrease in lumbar spine BMD in the group given calcium after 9 months of treatment compared with Pouills' study which showed a 2%

decrease in lumbar spine BMD in the group given calcium after 6 months of treatment(Pouilles, J. M., Tremollieres, F., et al, 1991).

The findings of the BMDs at the hip sites are similar to many previously reported observations(Riggs, B. L., Hodgson, S. F., et al, 1990; Pouilles, J. M., Tremollieres, F., Causse, E., et al, 1991; Zerwekh, J. E., Hagler, H. K., et al, 1994; Reginster, J. Y., 1995)(Table 4.5.). The BMDs of different hip sites have shown little or no significant changes with fluoride treatment with doses of 26.4 to 75 mg per day for 6 to 48 months. In our study, the decrease in femoral neck BMD in the group given Tridin is five folds(Pouilles, J. M., Tremollieres, F., et al, 1991), and eight folds of Pouilles' and Rizzoli' findings respectively(Rizzoli, R., Chevalley, T., et al, 1995).

In general, the BMDs of the hip decrease more rapidly than that of the lumbar spine(Table 7.4), and similar findings were observed for the group given calcium.

In our study, only 3 patients (10%) in the Tridin group showed increases in the lumbar spine BMD, whilst 8 patients (27%) in the calcium group showed increases in the lumbar spine BMD(Table 7.7, Figure 7.1). Other researchers have shown a 35% increase in lumbar spine BMD after 6 months of fluoride treatment. Some researchers have suggested that fluoride non-responders may have a different genotype resulting in lower oestrogen receptor activity(Kobayashi, S., Inoue, S. et al, 1996); and other researchers have reported that vitamin D receptor activity may also play a role in the regulation of BMD(Houston, L. A., Grant, S. F. A. et al, 1996). Genetic

variation in the activities of these receptors may result in the differences in response to fluoride.

Our study period of 9 months is relatively short. Previous studies last from 6 months to 6 years(Meunier, P. J., 1990; Riggs, B. L., Hodgson, S. F., et al, 1990; Pouilles, J. M., Tremollieres, F., et al, 1991; Riggs, B. L., WM, O. F., et al, 1994; Thiebaud, D., Burckhardt, P., et al, 1994; Rizzoli, R., Chevalley, T., et al, 1995). However, many of these studies showed change in BMD occurring within 6 months of fluoride treatment(Meunier, P. J., 1990; Riggs, B. L., Hodgson, S. F., et al, 1990; Pouilles, J. M., Tremollieres, F., Causse, E., 1991; Thiebaud, D., Burckhardt, P., et al, 1994; Rizzoli, R., Chevalley, T., et al, 1995). Our dosage of 20 mg fluoride is low compared with many other reported studies with dosages varied from 26.5 mg to 75 mg fluoride per day.

For our Tridin and its sub-groups, the BMD results were lower than that of the calcium alone sub-groups. It is believed that a high dose of (40-200 mg) fluoride can cause fluorosis, while low fluoride dosage of(20-40 mg) may induce bone formation. For example, it has been demonstrated that daily intake of 44.2 mg NaF or more can cause osteomalacia. The combination dosage of elemental fluoride and calcium(Tridin) in our study was based on the data from the Caucasian studies. Thus, the dosage might not be appropriate for Chinese patients.

In summary, some of the previously reported studies suggested that high dose of elemental fluoride results in a decrease of BMD while lower dose of elemental fluoride results in an increase of BMD. In our study, the

mean fluoride intake after adjusted for compliance was 12 mg / day, which is relatively lower when compared with other European studies(Riggs, B. L., Hodgson, S. F., et al, 1990; Meunier, P. J., 1990; Zerwekh, J. E., Hagler, H. K., et al, 1994). However, decreases in BMDs among the patients were observed. Possible explanations are that their calcium intake are not sufficient and / or the fluoride supplement is not optimum. Either too low or too high of fluoride concentration would affect bone formation. Hence serum fluoride measurement may be needed in order to confirm its bioavailability for bone formation. Many other researchers have shown that fluoride has a narrow therapeutic window, and this fluoride therapeutic window may vary with age and race.

Side effects of arthritis, fasciitis, acute lower extremity pain syndrome(Riggs, B. L., Hodgson, S. F., et al, 1990; Pouilles, J. M., Tremollieres, F., et al, 1991) are all factors that affect the patients' willingness to continue the treatment. In part the odour and size of the tablets may also reduce their compliances with treatment.

In addition, the high dropout rate reduced the power from 0.7 to less than 0.5. with a postulated statistical difference of 0.8 between the Tridin and the calcium groups. The high dropout rate also destroyed the permutation blocks, which in term reduced the degree of randomisation. Furthermore, scatter age distribution occurred in each block limited the randomisation. BMDs were affected by age, sex and BMI, hence, large sample size with a power of 0.8 and a lower postulated statistically difference was needed.

In order to improve the statistical power of the studies more patients will be needed and these patients can be recruited from different government clinics in Hong Kong. These potential subjects may be reviewed by a medical doctor in order to reduce the selection bias. Their medical records regarding to the past history of medication may be useful in determining their true exposure to inhaled steroids. Unfortunately, most people have had more than one general practitioner during their life-time. Hence, it is difficult to deduce their usage of different steroids.

Recall bias may be reduced in asking subject's daily calcium intake, if a diary form can be given to the potential subjects and request them to record their dietary intake.

A placebo group is needed in the Tridin and the calcium trial in order to determine the effect of calcium alone in this group of patients.

A large sample size is needed to improve the power of the study in order to further examine the effect of fluoride supplementation on bone mineral density

Chapter 10 Conclusion

The following conclusions may be drawn from our study.

1. Men and postmenopausal women with obstructive airway disease (OAD) but who are not on inhaled steroids have lower fat mass and percentage of body fat content compared with the age and BMI matched controls.

2. Men with OAD but who are not on inhaled steroids have statistically significant lower lean mass compared with the age and BMI matched controls.

3. Men or post-menopausal women with OAD on inhaled steroids have similar lean mass, body fat mass compared with OAD subjects who are not on inhaled steroids.

4. The BMDs of the total body, lumbar spine(L1-L4), femoral neck, intertrochanteric region and Ward's triangle of women OAD patients who are not on inhaled steroids are lower than age, and BMI matched controls. However, their differences are not statistically significant.

5. The BMDs of the total body, lumbar spine(L1-L4), femoral neck, intertrochanteric region and Ward's triangle of men OAD patients who are not on inhaled steroids are statistically significant lower than the age and BMI matched controls.

6. Inhaled steroids increase the body fat mass among premenopausal or postmenopausal female OAD patients compared with the age and BMI matched controls, but not in the men OAD patients with similar dose and duration of inhaled steroids treatment.

7. Inhaled steroids increase the fat mass among premenopausal and postmenopausal OAD female patients with similar magnitude.

8. Inhaled steroids do not affect the lean mass in OAD patients compared with the age and BMI matched controls.

9. Inhaled steroids do not affect the percentage of body fat content among women and men OAD patients compared with age and BMI matched controls.

10. The BMDs of the total body, femoral neck, intertrochanteric region and Ward's triangle of premenopausal female OAD patients on inhaled steroids are similar, but the BMD of the lumbar spine(L1-L4) is statistically significant lower than that of the age and BMI matched controls.

11. The BMD of the lumbar spine(L1-L4) of postmenopausal women OAD patients on inhaled steroids are statistically significant lower than that of the age and BMI matched controls.

12. The BMDs of the lumbar spine(L1-L4), femoral neck, intertrochanteric region and Ward's triangle of men OAD patients on inhaled steroids are statistical significant lower compared with the age and BMI matched controls.

13. The BMD at the lumbar spine(L1-L4) of men and post-menopausal women OAD patients on inhaled steroids are statistical significant lower as compared with the age and BMI matched men and post-menopausal women OAD patients not on inhaled steroids.

14. 52% of the Tridin treated patients had certain side effect compared with 34% of the calcium treated patients.

15. Intake of 12 mg fluoride and 371 mg calcium per day for nine months do not increase BMD when comparing with the group given 434 mg calcium alone. In fact,

both fluoride and calcium groups show decreases in mean BMDs of the lumbar spine(L1-L4), femoral neck, intertrochanteric region and Ward's triangle.

16. The percentage change of BMD is higher in the Tridin treated group.

17. A similar degree of bone loss between the Tridin and calcium treated groups is noted. However, bone loss more rapidly in men OAD patients treated with Tridin.

18. Site-specific bone loses due to Tridin treatment is found among men and premenopausal women OAD patients. Bone losses are more marked at hip compared with lumbar spine(L1-L4), but no site-specific bone loss with calcium treatment is observed.

Appendix 1: Questionnaire for OAD bone mineral density study

FACULTY OF MEDICINE
THE CHINESE UNIVERSITY OF HONG KONG
香港中文大學
醫學院

DEPARTMENT OF MEDICINE
PRINCE OF WALES HOSPITAL
SHATIN, N.T., HONG KONG
TEL: 2632 3126 / 2632 3127
FAX: (852) 2637 3852 / (852) 2637 5396
Your Reference:
Our Reference:

內科學系
香港新界沙田
威爾斯親王醫院
電話：二六三二三一二六
二六三二三一二七

The Effects of Fluoride on Bone Mineral Density in Chinese Obstructive Airway Disease(OAD) Subjects Suffering from Osteoporosis

Jointly organised by
Department of Medicine
Department of Community and Family Medicine
The Chinese University of Hong Kong

I hereby agree to participate in the above research project, including questionnaire interview, bone mineral density measurements, treatment, X-ray and follow-up study.

I understand that all information obtained will be merely for research purpose.

Signed: _____

Name: _____(Chinese)

_____(English)

HKID No.: _____

Date: _____

Appendix 1: Questionnaire for OAD bone mineral density study

1. Name: _____ (_____)

2. Address: _____ 3. Serial Number: _____

_____ 4. Weight: _____

_____ 5. Height: _____

_____

6. HKID Number: _____ 7. Tel no: _____

8. Hospital Number _____ 9. Date of birth: _____

Detailed data on disease, respiratory function and drugs
(To be extracted from medical records)

Lung Function Results
PFR
FEV1
VC

Age at first diagnosis of OAD 10. _____ for _____ years.

Concomitant medical conditions: write down all conditions

Drug history:

11. Steroids

a) Oral: Currently on oral steroids? (1=Y 2=N) 11a.___

_____ mg per day for _____ weeks
_____ mg per day for _____ weeks
_____ mg per day for _____ weeks

b) Inhaled: currently on inhaled steroids? (1=Y 2=N) 11b.___

_____ µg per day for _____ weeks
_____ µg per day for _____ weeks
_____ µg per day for _____ weeks

12. Other drugs, written down all current drugs where applicable.

Cigarette smoking and alcohol consumption

13. Smoker (1=current; 2=ex; 3=never) 13.____

14. If current or ex smoker, 14(a) cigarette per day for 14(b) years 14a____ b_____
then, 14(c) cigarette per day for 14(d) years 14c____ d_____
then, 14(e) cigarette per day for 14(f) years 14e____ f_____
Smoking 14(g) years; 14(h) cigarette pack year 14g____ h_____

15. Drinker? (1=current; 2=ex; 3=never) 15____

16. If drinker, for how many *16(i)* years and *16(ii)* days a week? 16*i*____ *ii*_____
How much a days

a) Beer (cans) 16a._____

b) Liquor (patts) 16b._____

c) Wine (glass) 16c._____

Physical activity . :

17 What is your longest occupation? 17.____

18. What is your present occupation? 18.____
(l=sedantary; 2=manual; 3=heavy manual)

19. How would you describe yourself when you were 20 years old ? 19.____
1) physical active 2) moderately active 3) physically inactive

20. Can you perform these activities now?(in between attacks) (Yes / No)

a) Walk on the level without feeling dyspnoeic 20.a.___

b) Walk uphill / upstairs without feeling dyspnoeic 20.b.___

c) Run without feeling dyspnoeic 20.c.___

21. In the last week, how many days in a week did you perform the following

a) Walking outdoors 21.a.___days

b) Walking up a mountain. 21.b.___days

c) Walking with a load (of 5 Kg or more) 21.c.___days

22 How many hours did you spends on the following activities last week?

a) Tai-chi 22a. _____ hours

b) Swimming 22b. _____ hours

c) Jogging 22c. _____ hours

d) Ballgames 22d. _____ hours

e) Dancing 22e. _____ hours

Calcium intake

23. Was last week a typical week in your life? If so, can you put down how many times you consume the following food-items last week 23. _____ ?

No. of average portion size each time times

a. Milk a._____

b. Milk powder b._____

c. Evaporated milk c._____

d. Soya bean milk d._____

e. Ovaltine or Horlick e._____

f. Ice cream f._____

g. Cheese g._____

h.	Soya bean curd	h._____
i .	Soya bean curd cheese	I._____
j.	Fish	j._____
k.	Shrimp	k._____
l.	Crab	l._____
m.	Dried fish	m._____
n.	Canned fish	n._____
o.	Green vegetables	o._____
p.	Bread	p._____
q.	Nuts	q._____

Average calcium intake _____ mg per day

24. When you were 20 years old, how often did you consume dairy products(milk, cream and cheese)? 24.____

1) never
2) daily
3) 2-3 times/week
4) less: than 1 time/week

Reproductive history

25.	How old were you when you first had your menstruation ?	25. _____
26.	Have you ever taken any oral contraceptives? (yes=1 no=2)	26. _____
27.	If yes, for how many months?	27. _____
28.	Do you still have menstruation? (yes=1 no=2)	28. _____
29.	If not, how many months ago did it stop ?	29. _____

History of fractures

30. Have you ever had any fracture?(yes=1 no=2) 30. _____
31. If yes, choose from the following 31. _____
    1). hip fracture
    2). forearm fracture
    3). vertebral fracture

32. Has your mother had any fractures? (yes = 1 no=2) 32. _____

33. If yes, which of these fractures did she have 33. _____
    1). hip fracture
    2). forearm fracture
    3). vertebral fracture

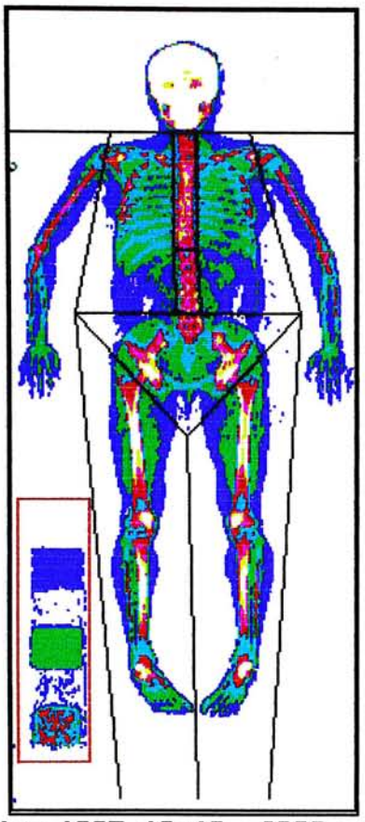
Appendix 2: Bone scans from Hologic QDR 2000

Figure A2.1 Scan image and print out for total body BMD

Right: Scan image and printout for total body bone mineral data, biography and essential quality control data from a OAD pre-menopausal patient.

Right: Scan image and printout for regional bone mineral data, biography and essential quality control data from a OAD pre-menopausal patient.

CUHK



·09.Nov.1995 10:12 [330 x 152]
Hologic QDR-2000 (S/N 2441)
Enhanced Array Whole Body V5.67A

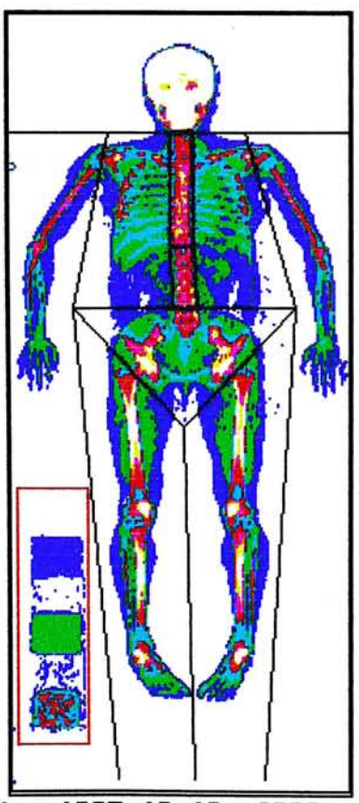
F1026950A Thu 26.Oct.1995 10:37
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: ML Weight: 62.70 kg
BirthDate: 29.Dec.55 Age: 39
Physician:
Image not for diagnostic use

TOTAL BMC and BMD CV is < 1.0%
C.F. 1.009 1.058 1.000

Region	Area (cm2)	BMC (grams)	BMD (gms/cm2)
L Arm	166.89	102.73	0.616
R Arm	164.88	106.16	0.644
L Ribs	114.61	62.21	0.543
R Ribs	151.61	87.92	0.580
T Spine	125.07	113.87	0.910
L Spine	67.16	67.37	1.003
Pelvis	178.15	190.79	1.071
L Leg	327.34	319.07	0.975
R Leg	334.58	323.96	0.968
SubTot	1630.29	1374.07	0.843
Head	251.34	564.41	2.246
TOTAL	1881.63	1938.48	1.030

HOLOGIC

CUHK



·09.Nov.1995 10:12 [330 x 152]
Hologic QDR-2000 (S/N 2441)
Enhanced Array Whole Body V5.67A

F1026950A Thu 26.Oct.1995 10:37
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: ML Weight: 62.70 kg
BirthDate: 29.Dec.55 Age: 39
Physician:
Image not for diagnostic use

TBAR552
F.S. 68.00% 0(10.00)%
Head assumes 17.0% brain fat
LBM 73.2% water

Region	Fat (grams)	Lean+BMC (grams)	% Fat (%)
L Arm	1433.4	1529.3	48.4
R Arm	1427.8	1541.6	48.1
Trunk	12424.1	19886.0	38.5
L Leg	4330.6	5367.9	44.7
R Leg	4488.9	5326.5	45.7
SubTot	24104.9	33651.4	41.7
Head	867.2	3848.7	18.4
TOTAL	24972.0	37500.1	40.0

HOLOGIC

Figure A2.1(continue)

Top: Data summary from body composition analysis and patient biography.

Bottom: Comparison with the normal range displayed as mean ± 2 SD with respect to age- and sex-matched normal subjects (Z - scores) and with maximum bone mass of the same population at young adult age (T - scores). The percentage figures give percent of the mean value of the reference population.

CUHK

Hologic QDR-2000 (S/N 2441)
Enhanced Array Whole Body V5.67A
·09.Nov.1995 10:12

F1026950A Thu 26.Oct.1995 10:37
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: ML Weight: 62.70 kg
BirthDate: 29.Dec.55 Age: 39
Physician:

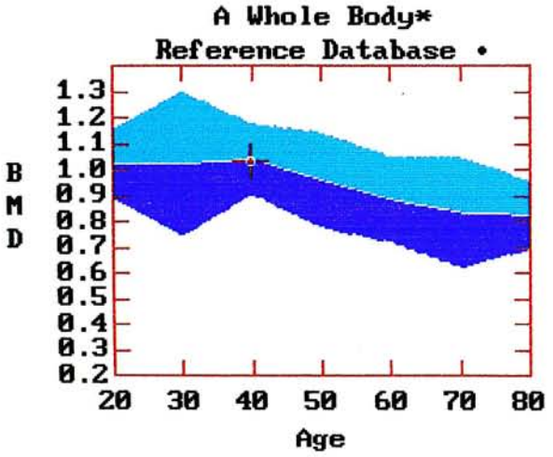
TBAR552
F.S. 68.00% 0(10.00)%

Region	BMC (grams)	Fat (grams)	Lean (grams)	Lean+BMC (grams)	Total (grams)	% Fat (%)
L Arm	102.7	1433.4	1426.6	1529.3	2962.7	48.4
R Arm	106.2	1427.8	1435.5	1541.6	2969.5	48.1
Trunk	522.2	12424.1	19363.9	19886.0	32310.1	38.5
L Leg	319.1	4330.6	5048.8	5367.9	9698.5	44.7
R Leg	324.0	4488.9	5002.5	5326.5	9815.4	45.7
SubTot	1374.1	24104.9	32277.3	33651.4	57756.2	41.7
~Head	564.4	867.2	3284.3	3848.7	4715.9	18.4
TOTAL	1938.5	24972.0	35561.6	37500.1	62472.1	40.0

~assumes 17.0% brain fat
LBM 73.2% water

HOLOGIC

CUHK



BMD(WHOLE) = 1.030 g/cm^2

T(49.0)		Z	
+0.62	106%	-0.20	99%

F1026950A Thu 26.Oct.1995 10:37
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: ML Weight: 62.70 kg
BirthDate: 29.Dec.55 Age: 39
Physician:

◆ Age, sex, and ethnicity matched
T Peak bone mass
Z = Age matched ML 19 Feb 97

HOLOGIC

Figure A2.2. Complete bone mineral report for the lumbar spine.

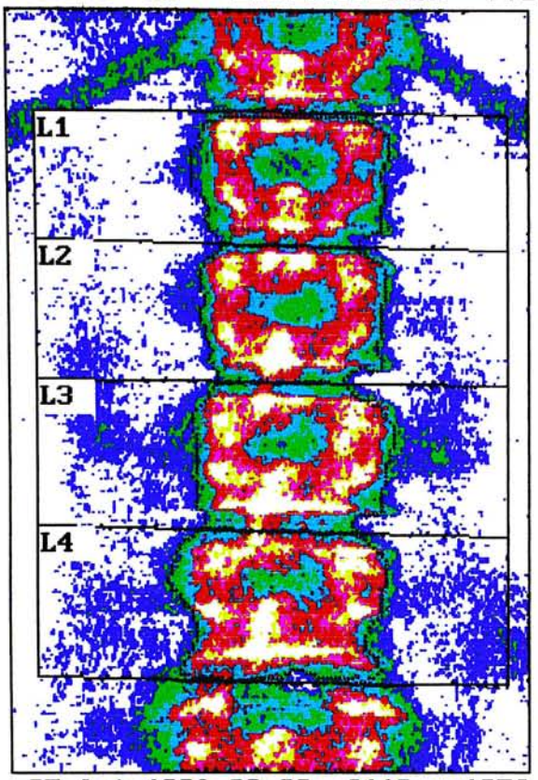
Top left: Bone mineral image with standard ROI including L1-L4.

Top right Biographical and information on bone area, BMC, and BMD. BMD is presented for each vertebra and for the entire ROI. Images and data on individual vertebrae are used to judge uniformity of bone mineral distribution.

Bottom: Comparison with the normal range displayed as mean ± 2 SD with respect to age- and sex-matched normal subjects (Z - scores) and with maximum bone mass of the same population at young adult age (T - scores). The percentage figures give percent of the mean value of the reference population.

CUHK

k = 1.235 d0 = 115.4(1.000H) 7.136



·27.Oct.1996 22:39 [113 x 137]
Hologic QDR-2000 (S/N 2441)
Array Spine Medium V4.74A:1

F05189519 Thu 18.May.1995 12:36
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:
Image not for diagnostic use

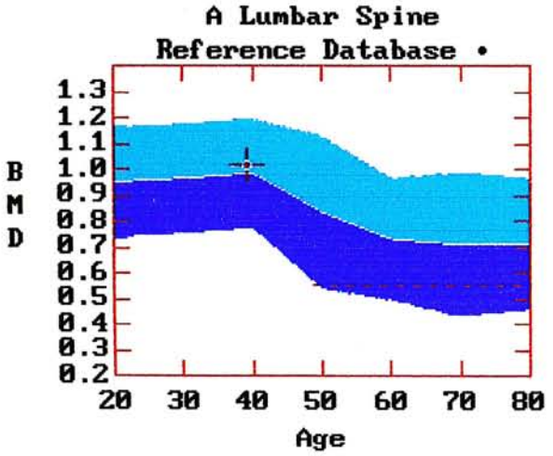
TOTAL BMD CV FOR L1 - L4 1.0%

C.F. 0.992 0.983 1.000

Region	Est.Area (cm^2)	Est.BMC (grams)	BMD (gms/cm^2)
L1	12.85	12.42	0.967
L2	12.86	13.15	1.023
L3	14.91	15.19	1.019
L4	15.65	16.07	1.027
TOTAL	56.27	56.84	1.010

HOLOGIC

CUHK



BMD(L1-L4) = 1.010 g/cm^2

Region	BMD	T(49.0)	Z
L1	0.967	+1.35 127%	+0.71 109%
L2	1.023	+1.17 122%	+0.38 104%
L3	1.019	+0.87 115%	+0.01 100%
L4	1.027	+0.78 113%	-0.11 99%
L1-L4	1.010	+1.06 118%	+0.20 102%

◆ Age, sex, and ethnicity matched
T=Peak Bone Mass
Z=age matched ML 25 Feb 97

F05189519 Thu 18.May.1995 12:36
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:

HOLOGIC

Figure A2.3. Complete bone mineral report of the left proximal femur

Top left: The ROIs as defined on Hologic instruments are shown:

1 femur neck ROI

2 Ward's triangle ROI

3 Trochanter ROI

4 Intertrochanter ROI

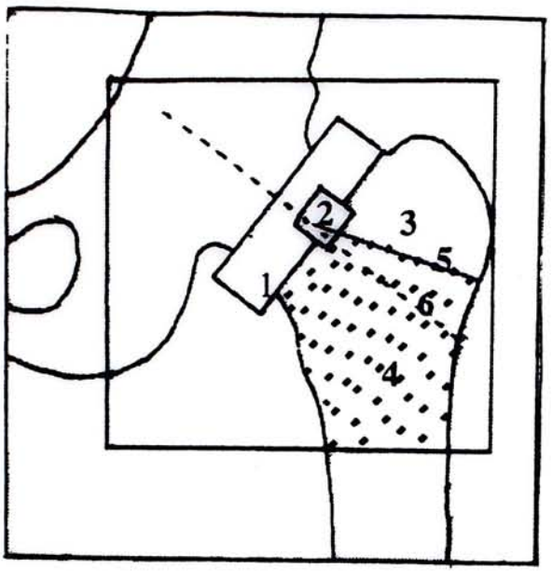
5 Centre line of femur neck

6 Inferior border of trochanter ROI

The entire area covered by neck ROI trochanter ROI and intertrochanter ROI is called the total ROI

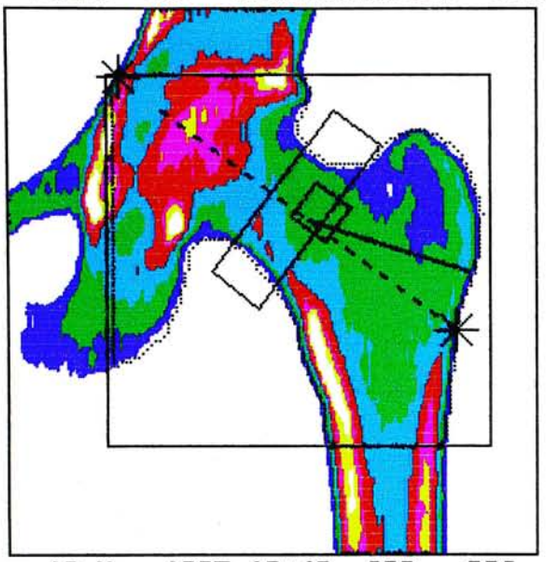
Top right: Biographical and information on bone area, BMC, and BMD are shown. BMD is presented for femur neck ROI, trochanter ROI, intertrochanter ROI, Total ROI, and Ward's triangle ROI.

Bottom: Comparison with the normal range displayed as mean ± 2 SD with respect to age- and sex-matched normal subjects (Z - scores) and with maximum bone mass of the same population at young adult age (T - scores). The percentage figures give percent of the mean value of the reference population.


1
2
3
4
5
6

CUHK

k = 1.247 d0 = 120.8(1.004H) 5.712



·18.May.1995 12:49 [92 x 89]
Hologic QDR-2000 (S/N 2441)
Array Left Hip Medium V4.59A:1

F0518951C Thu 18.May.1995 12:45
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:
Image not for diagnostic use

TOTAL BMD CV 1.0%
C.F. 0.992 0.983 1.000

Region	Est.Area (cm^2)	Est.BMC (grams)	BMD (gms/cm^2)
Neck	4.56	3.72	0.816
Troch	8.83	5.42	0.614
Inter	16.51	17.24	1.045
TOTAL	29.90	26.39	0.883
Ward's	1.12	0.73	0.653

Midline (96,106)-(166, 54)
Neck -49 x 15 at [25, 11]
Troch 15 x 39 AXIS 10.512 cm
Ward's -11 x 11 at [9, 4]

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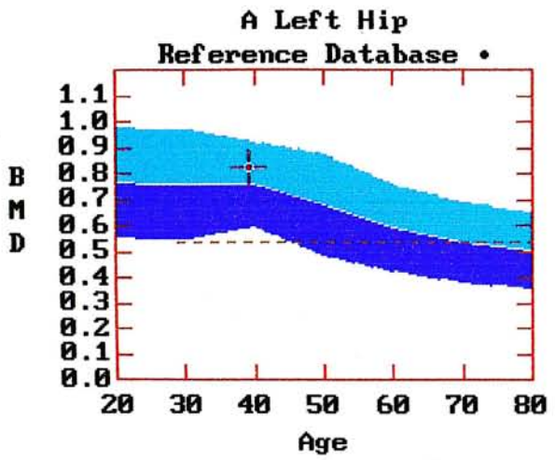


BMD(Neck[L]) = 0.816 g/cm^2

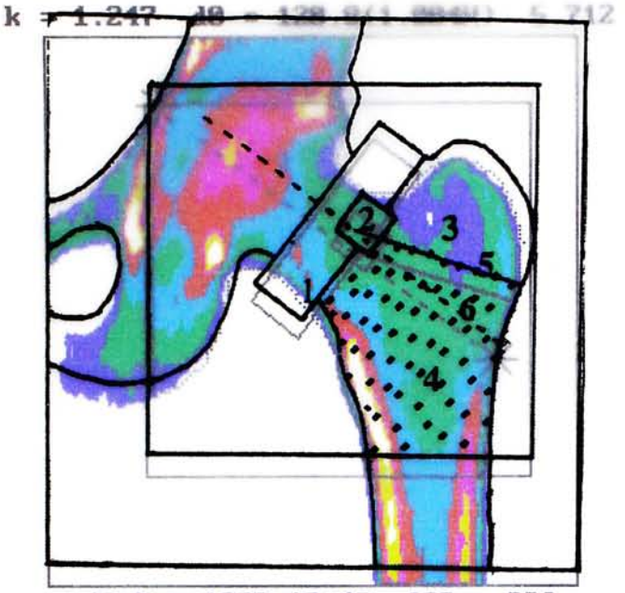
Region	BMD	T	Z
Neck	0.816	+0.47 107% (29.0)	+0.61 107%
Troch	0.614	+0.20 103% (49.0)	-0.63 92%
Inter	1.045	+0.84 112% (49.0)	+0.11 101%
TOTAL	0.883	+0.89 112% (49.0)	+0.09 101%
Ward's	0.653	-0.44 92% (29.0)	-0.24 96%

◆ Age, sex, and ethnicity matched
T = Peak bone mass
Z = Age matched ML 19 Feb 97

F0518951C Thu 18.May.1995 12:45
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:

HOLOGIC

CUHK



·18.May.1995 12:49 [92 x 89]
Hologic QDR-2000 (S/N 2441)
Array Left Hip Medium V4.59A:1

F0518951C Thu 18.May.1995 12:45
Name: AT-WONG YIM BING, ANNIE
Comment: AT
I.D.: E678274(8) Sex: F
S.S.#: - - Ethnic: K
ZIPCode: Height: 159.00 cm
Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:
Image not for diagnostic use

TOTAL BMD CV 1.0%
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Midline (96,106)-(166, 54)
Neck -49 x 15 at [25, 11]
Troch 15 x 39 AXIS 10.512 cm
Ward's -11 x 11 at [9, 4]

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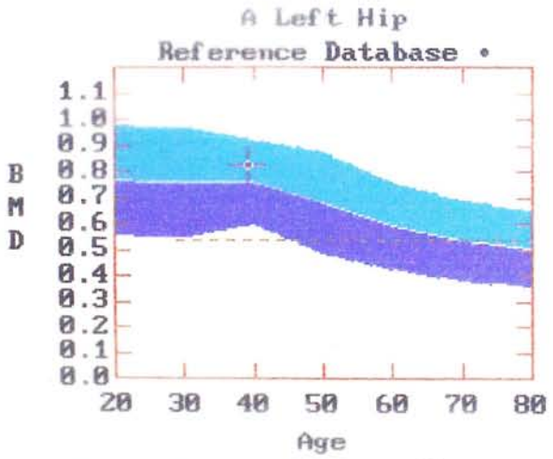

BMD(Neck[L]) = 0.816 g/cm^2

Region	BMD	T	Z
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TOTAL	0.883	+0.89 112% (49.0)	+0.09 101%
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◆ Age, sex, and ethnicity matched
T = Peak bone mass
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Scan Code: EL Weight: 61.30 kg
BirthDate: 29.Dec.55 Age: 39
Physician:

HOLOGIC

Appendix 3. Tables and reference curves for normal Hong Kong Chinese female or male BMD

Table A3.1. Total body BMD and lumbar spine(L1-L4) BMD for normal Hong Kong Chinese female

Age		Total body		Lumbar spine(L1-L4)	
(Year)	n	Mean	SD	Mean	SD
15-19	5	1.014	0.0666	0.950	0.0487
20-24	31	1.012	0.0741	0.943	0.1244
25-29	35	1.039	0.0605	0.969	0.1063
30-34	32	1.048	0.0706	0.971	0.1109
35-39	32	1.039	0.0664	0.966	0.1045
40-44	43	1.046	0.0666	0.990	0.1001
45-49	34	1.045	0.0797	0.993	0.1185
50-54	27	0.999	0.0824	0.899	0.1394
55-59	32	0.933	0.0980	0.788	0.1447
60-64	21	0.919	0.0831	0.763	0.0869
65-69	24	0.863	0.0827	0.712	0.1440
70-74	38	0.863	0.1415	0.735	0.1859
75-79	45	0.821	0.0739	0.697	0.0950
80-84	24	0.834	0.0702	0.730	0.1311
85-89	2	0.770	0.0099	0.610	0.0644

Table A3.2. Total body BMD and lumbar spine(L1-L4) BMD for normal Hong Kong Chinese female

Age		Femoral neck		Intertrochanteric region		Ward's triangle	
(Year)	n	Mean	SD	Mean	SD	Mean	SD
15-19	5	0.777	0.1017	1.066	0.1272	0.763	0.1220
20-24	32	0.768	0.0992	0.988	0.1075	0.746	0.1548
25-29	35	0.781	0.1180	1.045	0.1498	0.753	0.1403
30-34	32	0.763	0.1341	1.024	0.1622	0.716	0.1713
35-39	32	0.772	0.0823	1.036	0.1344	0.714	0.0976
40-44	43	0.775	0.0831	1.049	0.1038	0.701	0.1068
45-49	34	0.754	0.0869	1.016	0.1179	0.659	0.1215
50-54	27	0.730	0.0950	0.991	0.1069	0.590	0.1089
55-59	32	0.645	0.0933	0.874	0.1245	0.484	0.0976
60-64	21	0.631	0.0844	0.832	0.2115	0.472	0.0966
65-69	24	0.564	0.0802	0.801	0.1043	0.387	0.0882
70-74	38	0.569	0.0859	0.786	0.1488	0.382	0.1100
75-79	45	0.515	0.0699	0.710	0.1125	0.328	0.0813
80-84	24	0.514	0.0748	0.700	0.1248	0.317	0.0665
85-89	2	0.428	0.0842	0.553	0.0707	0.230	0.0495

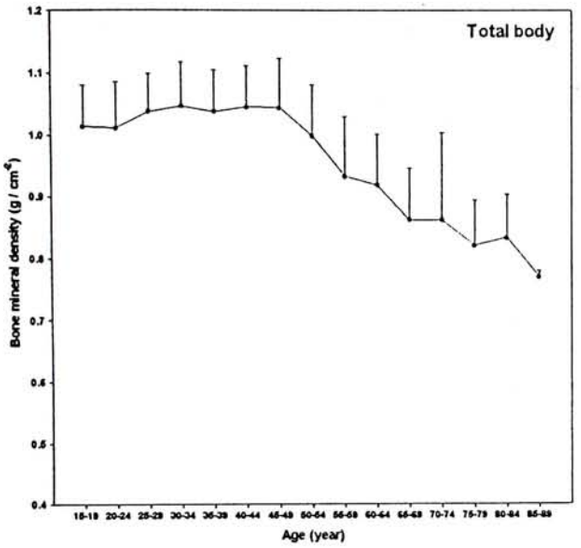
Table A3.3. Total body BMD and lumbar spine(L1-L4) BMD for normal Hong Kong Chinese male

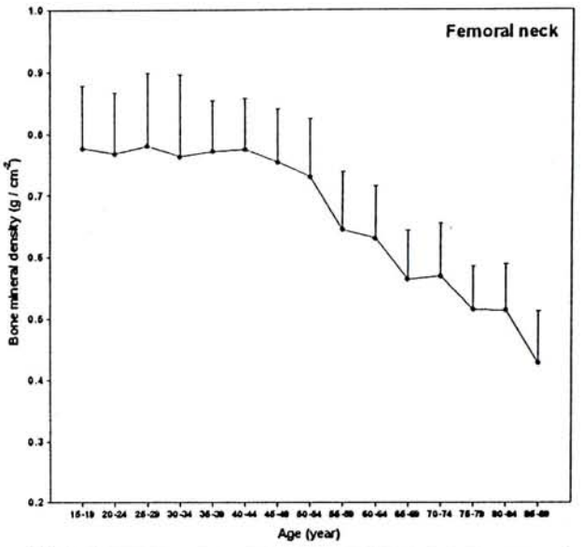
Age		Total body		Lumbar spine(L1-L4)	
(Year)	n	Mean	SD	Mean	SD
45-49	19	1.036	0.0795	0.915	0.1166
50-54	16	1.006	0.0604	0.859	0.1095
55-59	14	1.029	0.0633	0.906	0.0875
60-64	15	1.044	0.0968	0.884	0.1604
65-69	6	1.044	0.1447	0.998	0.1581
70-74	46	0.975	0.1612	0.879	0.1521
75-79	44	0.996	0.1261	0.941	0.1599
80-84	3	1.012	0.0367	1.035	0.1455

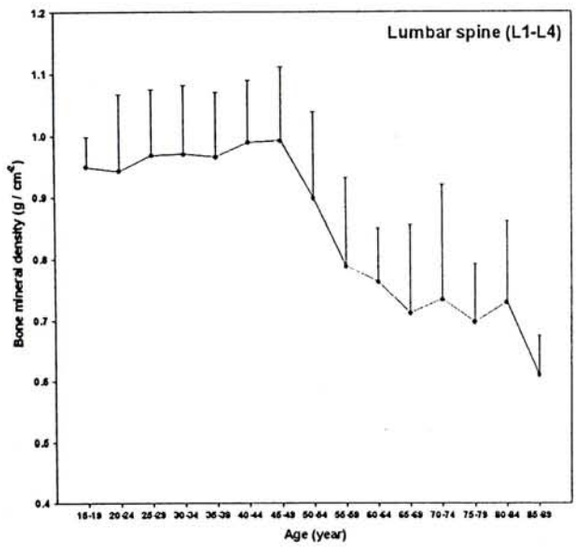
Table A3.4. Total body BMD and lumbar spine(L1-L4) BMD for normal Hong Kong Chinese male

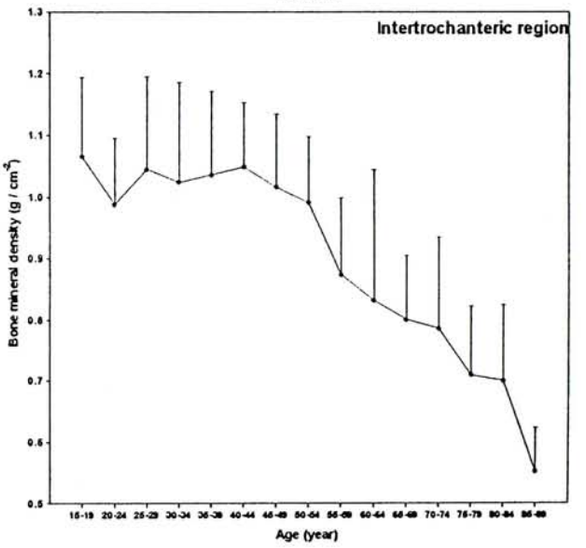
Age		Femoral neck		Intertrochanter		Ward's triangle	
(Year)	n	Mean	SD	Mean	SD	Mean	SD
45-49	19	0.733	0.0942	1.015	0.1131	0.577	0.1149
50-54	16	0.684	0.0940	0.917	0.2288	0.499	0.1061
55-59	14	0.723	0.0836	1.022	0.1106	0.564	0.1030
60-64	15	0.719	0.1452	0.953	0.1676	0.510	0.1403
65-69	6	0.692	0.1286	1.074	0.1919	0.513	0.1859
70-74	46	0.655	0.0996	0.931	0.1259	0.441	0.0953
75-79	44	0.663	0.0851	0.942	0.1327	0.444	0.0960
80-84	3	0.696	0.0285	0.993	0.0973	0.524	0.0585

Figure A3.1: Normal bone mineral density values (Mean,SD) for 425 Hong Kong Chinese females measured by Hologic QDR 2000 bone densitometry









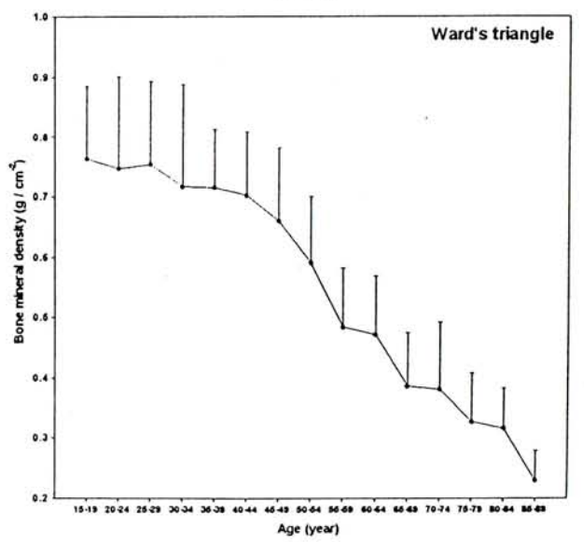
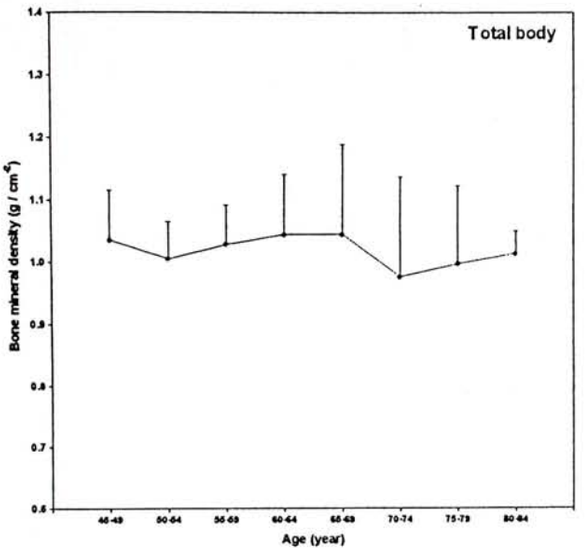
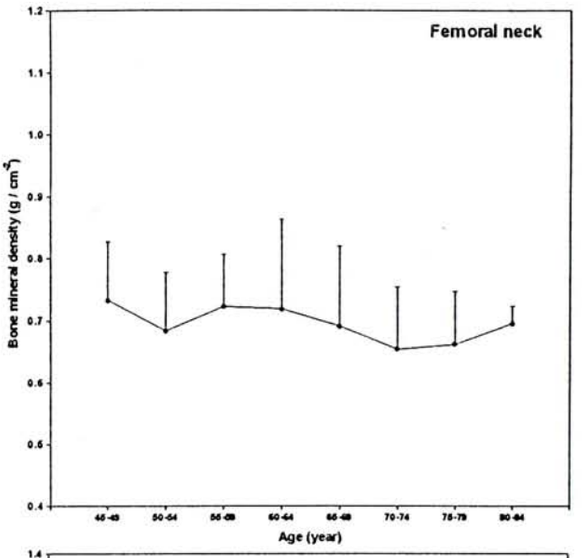
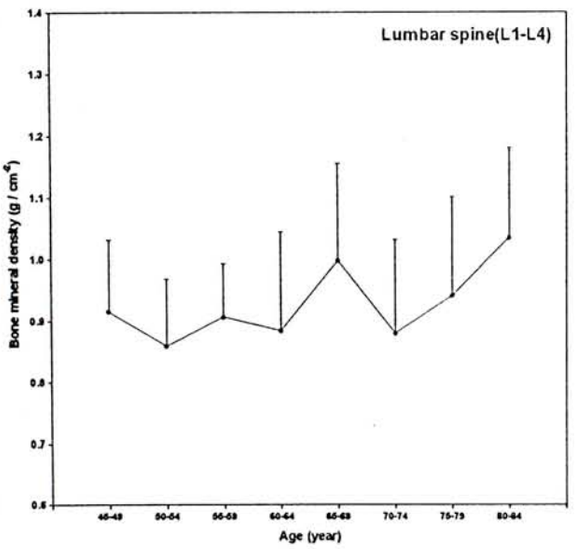
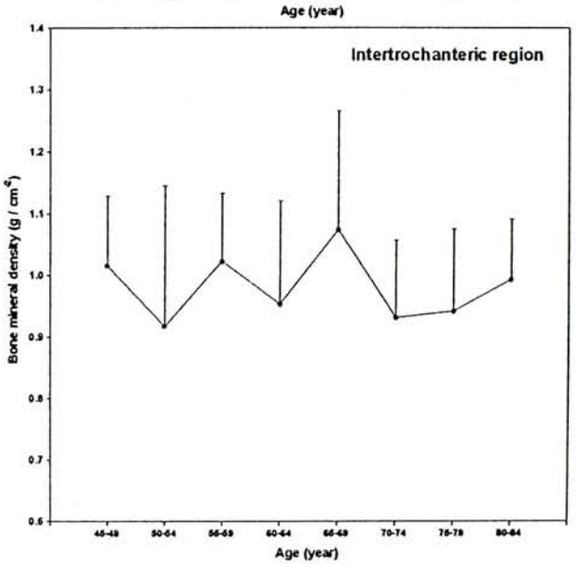


Figure A3.2: Normal bone mineral density values (Mean,SD) for 163 Hong Kong Chinese males age over 45 measured by Hologic QDR 2000 bone densitometry









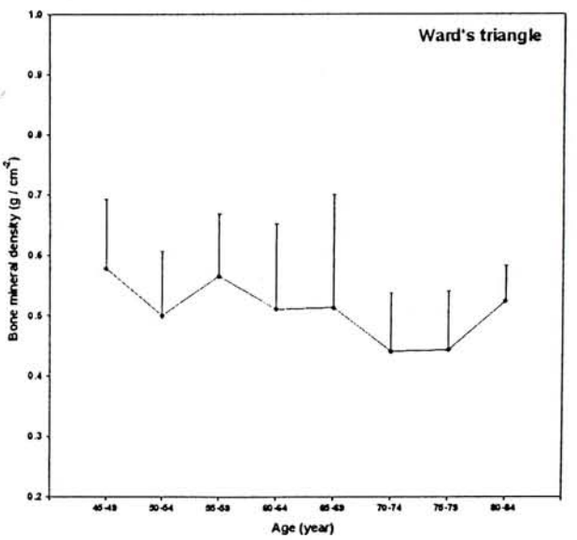


Table A 4. Correlations with age, BMD and anthropometric indices among OAD patients and control subjects

	Age	Duration of asthma	Height	Weight	BMI	Fat mass	Fat content (%)	Lean Mass	FEV1	FVC	Year of smoking	Cigarette pack year	Year of alcohol drinking	Alcohol intake mg/week	Age of menarche	Cumulative dose of oral steroid	Current Inhaled steroid dose	Cumulative dose of inhaled steroid	Total body BMD	Lumbar Spine BMD	Femoral neck BMD	Intertro-chanter BMD	Ward's triangle BMD
Age		-0.114	-0.038	-0.262*	-0.237**	-0.358***	-0.314**	0.030	-0.664***	-0.591***	0.423***	-0.010	0.111	0.091	0.358**	0.101	-0.373***	0.053	-0.450***	-0.540***	-0.692***	-0.633***	-0.800***
Duration of asthma	NA		-0.201**	0.010	0.127	0.103	0.125	-0.203*	-0.172	-0.194**	-0.208	-0.002	0.000	0.174	-0.002	0.097	0.274**	0.173	-0.090	-0.147	-0.040	0.020	-0.028
Height	-0.096	NA		0.353***	-0.213*	-0.088	-0.371***	0.640***	0.320***	0.444***	0.158	0.283*	0.321	0.205	-0.184	0.117	-0.045	-0.103	0.462***	0.413***	0.246**	0.240**	0.149
Weight	-0.102	NA	0.574***		0.834***	0.655***	0.488***	0.557***	0.370***	0.415***	-0.051	0.125	0.198	-0.164	-0.090	-0.136	0.199*	-0.048	0.251**	0.422***	0.566***	0.611***	0.412***
BMI	-0.061	NA	-0.057	0.781***		0.753***	0.739***	0.217*	0.178	0.156	-0.118	-0.040	0.110	-0.290	-0.045	-0.188	0.229**	0.030	0.002	0.195*	0.448***	0.499***	0.344***
Fat mass	-0.151*	NA	-0.077	0.581***	0.769***		0.932***	0.061	0.187	0.132	-0.236	-0.100	0.020	-0.118	-0.018	-0.035	0.331***	0.038	-0.118	0.185*	0.457***	0.470***	0.423***
Fat content	-0.182**	NA	-0.411***	0.281***	0.660***	0.792***		-0.248**	0.093	-0.003	-0.275*	0.236	-0.092	-0.124	-0.052	-0.022	0.376***	0.085	-0.244*	0.019	0.354***	0.367***	0.330***
Lean mass	0.080	NA	0.747***	0.681***	0.255***	-0.008	-0.405***		0.253*	0.417***	0.214	0.488***	0.307	0.020	0.020	0.015	-0.058	-0.148	0.413***	0.312**	0.234*	0.272**	0.077
FEV1S	NA	NA	NA	NA	NA	NA	NA	NA		0.864***	-0.157	0.056	0.212	-0.010	-0.370**	-0.226	0.141	0.017	0.559***	0.594***	0.608***	0.628***	0.667***
FVCS	NA	NA	NA	NA	NA	NA	NA	NA	NA		-0.157	0.217	0.143	-0.100	-0.411***	-0.179	0.142	-0.044	0.502***	0.546***	0.557***	0.564***	0.581***
Year of smoking	0.521***	NA	0.024	-0.358**	0.023	-0.427***	-0.368**	-0.129	NA	NA		0.385**	0.585**	0.357	0.145	0.290	-0.354**	-0.181	0.197	0.208	-0.176	-0.029	-0.184
Cigarette pack year	0.206	NA	0.270*	0.044	-0.044	-0.199	-0.398***	0.317**	NA	NA	0.270*		0.243	0.188	0.004	-0.144	-0.006	-0.267	0.239	0.176	0.031	0.154	-0.038
Year of drinking	0.491**	NA	0.182	0.118	0.023	0.078	0.007	0.078	NA	NA	0.137	-0.035		0.129	-0.682	0.335	-0.095	-0.067	0.181	0.068	0.147	0.176	0.037
Alcohol intake mg/week	0.126*	NA	0.179	0.067	-0.044	-0.093	-0.256***	0.240***	NA	NA	0.071	0.154	-0.062		0.341	0.507	-0.208	0.012	0.022	0.074	-0.169	-0.071	-0.110
Age of menarche	0.500***	NA	-0.262**	-0.245**	-0.134	-0.150*	-0.405	-0.211*	NA	NA	-0.261	-0.227	1.000***	0.057		-0.211	-0.059	0.052	-0.284*	-0.341**	-0.207	-0.333**	0.222*
Cumulative dose of oral steroids	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		0.232	0.274	-0.068	-0.345	-0.420*	-0.328	-0.313
Current dose of inhaled steroid	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		0.426***	0.102	0.065	0.265**	0.248**	0.267**
Cumulative dose of inhaled steroids	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		-0.118	-0.019	0.033	0.083	0.012
Total body BMD	-0.443***	NA	0.540***	0.471***	0.171**	0.056	-0.213***	0.523***	NA	NA	-0.176	0.161	0.244	0.088	-0.411***	NA	NA	NA		0.833***	0.658***	0.710***	0.633***
Lumbar spine BMD	-0.413***	NA	0.408***	0.467***	0.264***	0.165**	-0.035	0.402***	NA	NA	-0.074	-0.137	0.215	-0.009	-0.452***	NA	NA	NA	0.834***		0.752***	0.781***	0.733***
Femoral neck BMD	-0.565***	NA	0.399***	0.493***	0.302***	0.238***	0.075	0.371***	NA	NA	-0.445***	-0.019	0.190	0.021	-0.447***	NA	NA	NA	0.811***	0.756***		0.914***	0.922***
Intertrochanter BMD	-0.467***	NA	0.451***	0.542***	0.320***	0.252***	0.029	0.459***	NA	NA	-0.337**	0.043	0.182	0.061	-0.420***	NA	NA	NA	0.779***	0.752***	0.834***		0.849***
Ward's triangle BMD	-0.758***	NA	0.263***	0.313***	0.188**	0.206***	0.120*	0.170*	NA	NA	-0.453***	-0.149	0.117	-0.069	-0.479***	NA	NA	NA	0.761***	0.701***	0.911***	0.766***	

Values for OAD patients on inhaled steroid are given in the top right-hand part of the table, and those for age matched normal control subjects in the lower left-hand section

Two-tailed significance

* $p<0.05$

** $p<0.01$

*** $p<0.001$

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